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ORIGINAL ARTICLES

THE EFFECT OF MYOCARDIAL INFARCTION ON THE SIZE OF THE HEART*

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Data in the literature as to whether myocardial infarction *per se* can cause enlargement of the heart are contradictory (Master[17]). The majority of the reports are based on necropsy studies in which, by attempting to exclude an extracoronary mechanism for cardiac enlargement such as hypertension or valvular disease, the myocardial infarction was considered to have been entirely responsible for the enlargement. In other reports the heart was already enlarged when the clinical diagnosis of myocardial infarction was made. There are few studies in which a group of patients who had a myocardial infarction, with the heart normal in size at the onset, were roentgenologically observed for a prolonged period in order to determine whether cardiac enlargement subsequently ensued. If cardiac enlargement does result from a myocardial infarction there is little information as to how frequently this occurs and how long after the onset of the infarction the enlargement will appear.

The present report is a follow-up study of 489 patients who survived an acute myocardial infarction for at least 2 months and who had a normal-sized heart at the time of the infarction. Only those patients were included who had recovered from their presumed first infarction. All the cases were seen in private practice. Only patients with characteristic clinical and electrocardiographic evidence were selected and those in whom the onset of the infarction could be determined with certainty.

All patients were observed fluoroscopically; the majority had multiple examinations. In addition, 129 patients had one or more teleoroentgenograms which were used as a check for con-

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firmation of the fluoroscopic examination. The cardiothoracic ratio was used as an index of the heart size and the heart was considered to be enlarged when the total of the transverse diameters was more than half the internal diameter of the thorax. There were 4 necropsies which confirmed the clinical impression of the heart size.

TABLE 1.—AGE AND SEX INCIDENCE
(489—Total Number of Cases)

Age (Years)	*Male*	*Female*
>30	3	
30–39	28	
40–49	108	11
50–59	187	20
60–69	105	8
70–79	16	2
80+	1	
Total	448	41 = 489

TABLE 2.—DURATION OF OBSERVATION

Duration	*No. of Cases*
3–5 months	73
6–11 "	49
1–2 years	87
2–3 "	57
3–4 "	39
4–5 "	27
5–6 "	40
6–7 "	28
7–8 "	14
8–9 "	24
9–10 "	13
10–11 "	6
11–22 "	32
Total	489

Table 1 shows the age and sex incidence of the 489 cases. There were 448 males, or 91.6% of the total. It was to be expected that the large majority of the patients would be males, due to the greater frequency of hypertension in women who have a myocardial infarction. This, in turn, will cause a higher incidence of cardiac enlargement at the onset of the infarction and such cases were excluded from the study. The age incidence showed the usual peak incidence from the fifth through the seventh decades.

Table 2 shows the duration of observation. The majority of the patients were observed from 1 to 10 years. Four patients had Roentgen examinations, 18, 19, 21 and 22 years respectively, after the onset of the infarction.

Forty-four patients survived another myocardial infarction for at least 2 months. The average period of time between the initial attack and the last Roentgen examination was 29 months. Three patients were observed 7, 12 and 44 months respectively, after survival of a third infarction.

Cardiac enlargement developed in 25 patients. Fifteen patients had the usually accepted etiologic factors which could cause the enlargement: hypertension, 13 cases; calcification of aortic valve, 1 case; and unexplained cor pulmonale, 1 case. Two additional patients developed cardiac enlargement 3 years, eight months, and 4 years, respectively, after the last examination during which time they did not consult a physician, hence blood pressure determinations were not available.

There remain 8 cases, or 2% of the total, in whom the myocardial infarction could have been responsible for the enlargement. The patients were between the ages of 45 to 72 years and there was only one woman. The earliest observed appearance of the cardiac enlargement after the onset of the infarction was 6 months; the longest was 13 years. The exact onset of the enlargement could not be determined with certainty since the interval between Roentgen examinations, before the cardiac enlargement was noted, was variable. It ranged from 6 months to 4 years.

In 2 patients there was a progres-

sive increase in the enlargement, each of whom did not have interval examinations for 2 years. Congestive heart failure was present in all the cases but there was evidence that it preceded the enlargement in 4, all of whom had a myocardial aneurysm. Four patients survived a second myocardial infarction and cardiac enlargement was first noted 7 months to 3 years after the onset of the second infarction during which time there were repeated examinations.

Case reports of the eight cases are summarized.

Case Reports. CASE 1. B.B. is a man, 72 years of age. On January 18, 1950, at onset of infarction, the cardiothoracic ratio was normal; January 18, 1951, there was slight increase in transverse diameters but the cardiothoracic ratio was still within normal limits; November 18, 1952, same as previous examination; May 12, 1953, further increase in the heart size, exceeding the normal cardiothoracic ratio; July 26, 1955, left ventricle markedly enlarged. The clinical course was characterized by congestive failure from onset of infarction.

CASE 2. A.G. is a man, 45 years of age. Eleven days before onset of infarction heart was normal in size. Five months and two weeks later there was cardiac enlargement; the left ventricle reached almost to the left lateral wall of the thorax. Clinical course was characterized by congestive failure from onset of infarction.

CASE 3. R.S. is a woman, 46 years of age. On July 5, 1949, five months after onset of the infarction, the cardiothoracic ratio was within normal limits. On March 17, 1950, there was increase in the transverse diameters just beyond normal limits. On June 7, 1955, the teleoroentgenogram showed marked cardiac enlargement, the cardiothoracic ratio being 16.1:25 cm. Intermittent congestive failure was present from the onset of the infarction.

CASE 4. J.O., is a man, aged 64. Seven months after the myocardial infarction which occurred on May 3, 1941, the heart was normal in size. On November 30, 1943, there was no change. On March 14, 1949, the cardiothoracic ratio was within normal limits but a small aneurysm of the left ventricle was noted. On September 29, 1953, there was marked enlargement of the heart. The heart findings at the necropsy on December 24, 1954 were: "Heart weighs 750 gm. The enlargement is both hypertrophy and dilatation. Posteriorly there is an aneurysmal dilatation of the left ventricle involving approximately one-third of the posterior surface of the heart." The course was characterized by intermittent congestive failure from the onset with frequent attacks of pulmonary edema.

CASE 5. B.F., is a man, 55 years of age. On October 12, 1943, one month after onset of the myocardial infarction, the cardiothoracic ratio was within normal limits. During the following 9 years repeated fluoroscopic examinations revealed no change in the size and shape of the heart. On June 10, 1952, patient had another myocardial infarction and 2 months later a small myocardial aneurysm was noted but there was no increase in the transverse diameters. On May 16, 1955, a teleoroentgenogram revealed a cardiothoracic ratio of 14.8:30 cm. During the following year symptoms and signs of concongestive failure appeared which have persisted with varying intensity to the time of this report. On May 24, 1956, the cardiothoracic ratio was 15.5:30 cm.

CASE 6. E.Z. is a man, 54 years of age. During the first 11 years after the onset of the infarction (July 2, 1944) the heart was normal in size and shape on numerous fluoroscopic examinations. On February 16, 1953, there were symptoms and signs of congestive failure. Fluoroscopy revealed slight "rounding" of the left ventricle with a small myocardial aneurysm. On May 3, 1955, the cardiothoracic ratio was 15.8:32 cm. On May 10, 1956, the ratio was 17.2:32 cm. The congestive failure has persisted with varying intensity until the time of this report.

CASE 7. C.S. is a man aged 46 years. One month after the myocardial infarction which occurred on April 19, 1948, the heart was normal in size. Seven years later on April 1, 1955, there occurred another myocardial infarction. A teleoroentgenogram on April 27, 1955, showed a cardiothoracic ratio of 15:30 cm., and it was thought a small aneurysm was noted at the tip of the left ventricle. Two months later, symptoms and signs of cardiac decompensation appeared and they have persisted with varying severity to the time of this report. On May 8, 1956, the teleoroentgenogram showed a cardiothoracic ratio of 16.5:30 cm.

CASE 8. J.H. is a man, aged 50 years. The first myocardial infarction occurred on Janu-

ary 10, 1948. Fluoroscopic examinations until the onset of another myocardial infarction on June 11, 1950, showed the heart to be normal in size and shape. Two months after the second infarction a small myocardial aneurysm was noted at the apex of the left ventricle. Four months later symptoms and signs of cardiac decompensation appeared which have persisted with varying severity until the time of this report. On June 20, 1955, a teleoroentgenogram showed a cardiothoracic ratio of 17.5:31 cm.

There are few reports analogous to the present study. Sutton and Davis[25] showed by serial roentgenograms and postmortem studies of the heart that experimental coronary occlusion and myocardial fibrosis do not lead to generalized cardiac hypertrophy in animals even when they are subjected to strenuous exercise, though localized aneurysms of the ventricle developed under such conditions. Some of the animals were observed from 70 to 319 days. Horine and Weiss[13] reported that 20 patients who had normal-sized hearts at the time they experienced a coronary thrombosis did not develop roentgenologic evidence of cardiac enlargement although they were observed subsequently from 5 months to 9½ years. Massie and Miller[16] followed by Roentgen-ray studies 16 patients with acute coronary thrombosis from one week to 7 months with an average for the entire group of 4.7 months. Of the entire series, only one patient showed an increase in the heart size of 2 cm. which gradually increased to 2.9 cm. at the end of 6 months. In this particular case there is no mention either of the blood pressure or whether the heart was initially enlarged.

In contrast to the above studies, Katz and others[14] found that experimental coronary atherosclerosis in rabbits produced cardiac hypertrophy. They excluded atherosclerosis of the aorta, systemic arterial hypertension, aortic valvular defects, inflammatory disease of the myocardium and other actions of the diet as factors in the production of the cardiac hypertrophy. Smith and Bartles[23] report a case of myocardial infarction which presumably caused cardiac hypertrophy: a man 35 years of age was seen in congestive failure; the blood pressure had never been elevated and a year before he was observed by them, a roentgenogram showed that the heart was not enlarged. They state that coronary thrombosis with infarction may produce marked enlargement in a relatively short time. Master, Dack and Jaffe[18] cite one case: repeated teleoroentgenograms had showed a normal-sized heart. After an attack of pulmonary edema, initiated by a coronary thrombosis, there was sudden enlargement of the cardiac shadow which persisted after recovery from the thrombosis.

Palmer[21] found enlargement to develop in 8 patients who had normal-sized hearts when first examined radiologically. In 4 patients who did not develop hypertension the enlargement was considered due to coronary sclerosis itself. Two patients developed mild hypertension which could have caused the enlargement. In 2 others the cause could not be determined. In none of these cases is there information as to how long after the initial observation the increase in size developed. In 72 patients who had normal-sized hearts after the initial myocardial infarction, the heart remained normal in size. In them, the average period elapsing between the attack and the last Roentgen examination was more than 3 years; in 18 it was more than 5 years. Boas and Boas[5] state: "We have had many patients under treatment before the appearance of symptoms of coronary disease when they had neither hypertension nor cardiac enlargement, whose hearts in

the years following one or more myocardial infarcts became very large." Boas[4] observed 124 patients with coronary artery disease for at least 10 years. In 10 patients who never had hypertension, cardiac enlargement, as determined by fluoroscopy, seemed to develop directly after a myocardial infarction.

Discussion. It is evident that cardiac enlargement due solely to a myocardial infarction is rare; only 2% in our experience. The cause is very speculative since various possible mechanisms are operative, sometimes combined in the same patient. It is our opinion that a myocardial aneurysm which may develop at any time, even years after the onset of the myocardial infarction, or extensive myocardial fibrosis, or both, weakens the left ventricle. When congestive failure which is a common complication of both these conditions develops, the heart hypertrophies through as yet unexplained mechanisms. The congestive failure may be gradual in onset or may be precipitated by another infarction. All our cases had congestive failure.

It is impossible in most of our cases to determine how much of the increase in the heart size was due to hypertrophy of the left ventricle or was due to dilatation of this chamber from a ventricular aneurysm. The one certain exception was Case 4 which at necropsy showed not only a myocardial aneurysm but marked hypertrophy of the left ventricle. Schwedel[22] has commented on the difficulty of differentiating a myocardial aneurysm which involves a large portion of the left ventricle from other types of left ventricular enlargement. Gross and Schwedel[12] state that the enlargement of the heart due to a ventricular aneurysm is localized and that generalized enlargement not attributable to other causes is due to hypertension. In their cases without congestive failure there was no cardiac hypertrophy. They also found that when the heart with a myocardial aneurysm is hypertrophied, the bulge of the aneurysm did not appear to contribute to the increase in heart weight.

Varied explanations are given by others for the cause of the cardiac hypertrophy which presumably can be due to myocardial infarction. Anoxemia of the myocardium such as is used to explain the cardiac hypertrophy accompanying congenital anomalies of the coronary arteries (Bland, White and Garland[3], and Kaunitz[15]) is mentioned (Master[17]). Katz *et al.*[14] claim that the ischemia of the myocardium secondary to the induced coronary atheromatosis caused the cardiac hypertrophy in their experiments but the exact *modus operandi* was unknown. Others mention congestive heart failure as the sole explanation. Davis and Blumgart[8] postulated that with severe coronary sclerosis some hypertrophy results from impaired nutrition which causes the myocardial fibers to stretch and that the hypertrophy is greater in cases of congestive failure. Sohval and Friedberg[19] studied the hearts at necropsy of 100 cases of acute coronary occlusion. They excluded cases with associated cardiac disease or hypertension. Cardiac hypertrophy was absent in every case of acute coronary occlusion without evidence of hypertension or associated cardiovascular disease, unless there were distinct clinical or pathologic signs of congestive heart failure. The case cited by Smith and Bartels[23] developed cardiac hypertrophy in the course of congestive failure. Master *et al.*[18] also state that the cardiac enlargement observed in some patients with coronary thrombosis may be attributed to the congestive heart failure although it can also appear without gross heart failure

(Master[17]). Others have found a correlation between the size of the heart and congestive failure in patients with myocardial infarction (McCain, Kline and Gilson[19]).

Palmer[21] doubts that congestive failure can cause a permanent increase in heart size and attributes the enlargement to "chronic myocardial ischemia." Boas[4] states that it is probably a compensatory mechanism explained by Starling's law of the heart. Impaired nutrition leads to increased diastolic length which if continued over a sufficient period of time eventually may lead to hypertrophy (Starling and Visscher[24]). In some of Boas' cases the cardiac enlargement developed without manifestations of gross heart failure. Willius[26] states that existent cardiac hypertrophy may become marked through multiple infarcts. Miller and Weiss[20] suggested that when unexplained cardiac hypertrophy accompanies disease of the coronary arteries one should search for undeveloped collateral coronary circulation. Smith and Bartels[23] state that the enlargement does not appear to be a true hypertrophy in the sense that hypertrophy is taken to mean enlargement of individual muscle fibers. Yater and others[27] state that myocardial degeneration can cause cardiac hypertrophy, but that the true explanation for the hypertrophy is debatable. Connolly and Littmann[7] offer the following mechanism: coronary inadequacy which leads to impaired nutrition of muscle fibers provides an injury which causes dilatation and hypertrophy. This is the same explanation offered by Barron[1] based on the experimental work of Eyster[9].

In contrast, Gross *et al.*[11] who did not find any evidence that uncomplicated coronary artery disease can cause cardiac hypertrophy cannot conceive of the need for generalized cardiac hypertrophy as a compensatory mechanism for an infarcted myocardium. Bell and Clawson[2] find it difficult to believe that a compensatory hypertrophy of the heart can develop in the presence of an obviously decreased blood supply. Clawson[6] disputes the theory that compensatory hypertrophy of heart muscle follows myocardial fibrosis. He found that microscopic myocardial fibrosis was as common in hearts with coronary sclerosis but normal in size as in those with an equal degree of sclerosis but hypertrophied. He also doubted that hypertrophy can be due to ischemia of the heart muscle and cites 14 cases of syphilitic narrowing of the coronary orifices without syphilitic valvulitis, none of whom had cardiac hypertrophy.

There is little evidence that multiple myocardial infarctions can cause cardiac hypertrophy. Palmer[21] reported that one patient whose heart was enlarged showed an increase in size following a second attack of coronary thrombosis 18 months later. But he also noted that 7 patients who had more than one myocardial infarction did not develop cardiac hypertrophy. McCain, Kline and Gilson[19], who claim that coronary sclerosis and myocardial infarction *per se* may cause enlargement of the heart, found no correlation between the incidence of multiple infarction and heart size. In our study only 4 of the 44 patients who survived a second infarction developed cardiac enlargement a variable number of months and years after this second infarction but all had complicating congestive failure.

Summary. A roentgenologic follow-up study was made of 489 patients who survived an acute myocardial infarction for at least 2 months and who had a normal-sized heart at the time of the infarction. Only those patients were

included who had recovered from their presumed first infarction.

The majority of the patients were observed from 1 to 10 years.

Two per cent (8 cases) developed cardiac hypertrophy in the absence of generally accepted factors such as hypertension, valvular heart disease or cor pulmonale.

Cardiac enlargement was first noted from 6 months to 13 years after the onset of the infarction.

All 8 patients who developed cardiac hypertrophy had associated congestive heart failure.

Multiple myocardial infarctions did not cause cardiac hypertrophy in the absence of congestive failure.

The opinion is expressed that cardiac hypertrophy develops with congestive failure, which in turn results from a myocardial aneurysm or extensive myocardial fibrosis, or both, complications of the myocardial infarction.

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(Interlingua on page 144)

TREATMENT OF DIGITALIS TOXICITY BY CHELATION OF SERUM CALCIUM

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The increased use of digitalis glycosides in place of cruder preparations such as leaf has accentuated the problem of toxicity (Burwell and Hendrik[6], and Flaxman[9]), for with certain glycosides, such as digitoxin, cardiac arrhythmias are often the first sign of overdosage, and gastrointestinal symptoms may be inconspicuous or lacking. A further factor contributing to the problem of digitalis toxicity is the frequent concurrent use of diuretics which cause increased urinary excretion of potassium as well as sodium (Lown and Levine[22]).

Potassium depletion (Lown and Levine[22]) and calcium excess (Bower and Mengle[4], Gold and Kwit[14], and Baker and Baker[1]) enhance the toxic effects of digitalis. Conversely potassium administration, both experimentally (Lown *et al.*[23] and Page and Real[24]) and clinically (Sampson, Alberton and Kondo[26]), and calcium deficit produced in animals (Page and Real[24], and Smith and Grinnell[27]), have been found to prevent or abolish digitalis induced arrhythmias. Oral potassium salts are not well tolerated (Flear, Hill and Thomas[10]) and are inadequate for management of serious arrhythmias which require prompt therapeusis. Intravenous potassium must be administered with great caution, particularly in patients with heart disease because of the depressant effect of hyperkalemia on the heart.

Rapid induction of hypocalcemia may be accomplished by intravenous administration of sodium citrate (Bunker *et al.*[5]), or the chelating agent ethylenediamine tetraacetic acid (Bechtel, White and Estes[2], and Popovici *et al.*[25]). The following case reports indicate that various digitalis induced arrhythmias can be promptly and effectively abolished by the intravenous use of disodium salt of ethylenediamine tetraacetic acid. In addition the magnesium salt of EDTA has been employed to achieve the combined effect of lowering of serum calcium and elevation of serum magnesium. Magnesium antagonizes the physiological actions of calcium (Grollman[15]), and, administered intravenously as magnesium sulfate has been found effective in abolishing arrhythmias induced by digitalis (Szekely and Wynne[28]).

Case Reports. CASE 1. A.D., a 30-year-old woman with rheumatic heart disease (mitral stenosis and insufficiency) had had three episodes of congestive heart failure over a 5-year period preceding her current hospital admission, each of which responded to digi-

talis and a low salt regimen. Three days prior to her hospital admission, because of increasing dyspnea ,and orthopnea the patient digitalized herself without consulting a physician, taking 2.0 mg. of digitoxin over a 3-day period. She entered the hospital in congestive heart failure, with an irregular heart rate of 130 per minute. An electrocardiogram revealed paroxysmal atrial tachycardia with varying atrioventricular block and runs of bundle branch block simulating periods of ventricular tachycardia (Figs. 1*a*, *b*).

Six hundred milligrams of the disodium salt of EDTA was given intravenously in 250 ml. of 5% glucose in water. After 100 ml. had been infused in a 15-minute period the

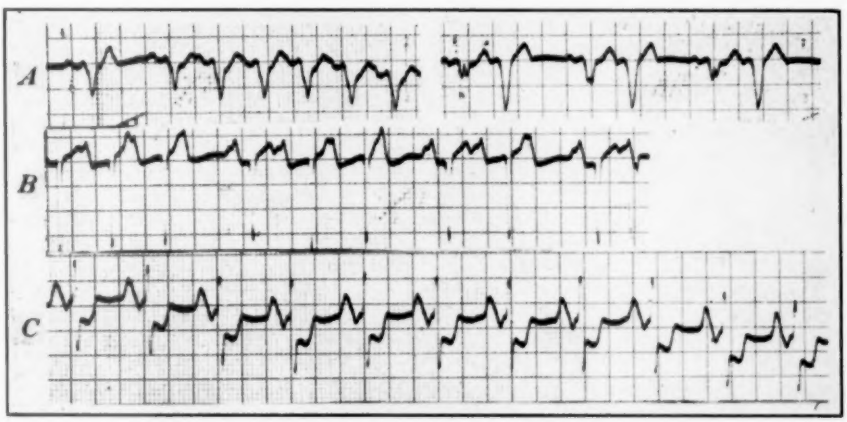

Fig. 1.—Effect of EDTA on digitalis induced arrhythmia. Strips *A*) leads 2 and aVf, and *B*) lead 1, before EDTA; strip *C*) lead 2, during EDTA infusion.

arrhythmia disappeared and sinus rhythm, rate 104, was present (Fig. 1*c*). Coincident with the restoration of normal rhythm noticeable clinical improvement occurred. Râles, which initially were audible in the lower half of both lung fields had disappeared by the time the infusion had been completed in a 30-minute period. The initial serum calcium level, prior to infusion of EDTA was 9.8 mg. per 100 ml., a half hour after completing the infusion the serum calcium level was 8.5 mg. per 100 ml. The arrhythmia did not recur over a 17-day period of observation. Digitoxin in dosage of 0.1 mg. daily was resumed 3 days after conversion of the arrhythmia and the patient was also maintained on potassium chloride, 0.67 gm. three times daily.

CASE 2. C.M., a 58-year-old woman had been hospitalized 17 times in a 5-year period for recurrent episodes of right and left sided heart failure due to hypertensive heart disease. There had been great difficulty in controlling the patient with digitalis because of the propensity to develop bigeminal extrasystoles. On admission to the hospital the patient was in severe congestive failure, apprehensive, dyspneic, cyanotic and orthopneic, cold and sweaty. Râles were present up to the fourth intercostal space posteriorly, venous pressure was markedly elevated, the liver was enlarged to 2 cm. above the iliac crest, and there was anasarca of the lower half of the body. Blood pressure was 220/94. An electrocardiogram (Fig. 2*a*) showed atrial fibrillation with bigeminal ventricular beats. The patient had been maintained prior to admission on 0.25 mg. digitoxin daily, and had been nauseous for a few days.

Six hundred milligrams of disodium EDTA was given in 250 ml. of 5% glucose in water within a half-hour period. After 70 ml. had been infused in a 10-minute period the extrasystoles disappeared, and did not recur thereafter (Figs. 2*b*, *c*). Concurrent with disappearance of the extrasystoles, which were frustrate contractions, there was marked clinical improvement with clearing of râles, and lessening of cyanosis, dyspnea, and orthopnea. Serum calcium initially 10.1 mg. per 100 ml., was 9.1 mg. per 100 ml. one hour after the infusion, and 9.0 mg. per 100 ml. 24 hours later. Five days later the patient was started on maintenance gitalin and was given KCl 2 gm. daily in divided doses. Her radio-

iodine uptake was found to be 72% and she was given radioiodine therapeutically.

CASE 3. M.M., a woman of 74 had had arteriosclerotic heart disease for an indeterminate period. She entered the hospital in congestive heart failure, and due to a language barrier, it was not learned until later that she had been receiving 0.2 to 0.3 mg. of digitoxin daily for several months. Digoxin (1.0 mg.) was given orally followed by 0.8 mg. of lanatoside C (Cedilanid). An hour later bigeminal rhythm was noted and the patient's clinical condition had worsened, with severe dyspnea, orthopnea, cyanosis, apprehensiveness and a cold sweat. An electrocardiogram revealed atrial tachycardia with varying block, and runs simulating bigeminal extrasystoles (Fig. 3).

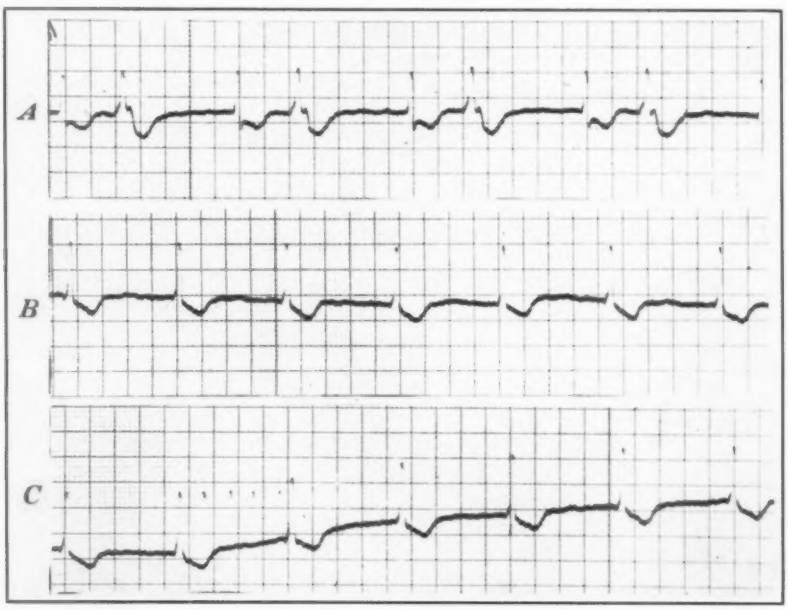

Fig. 2.—Effect of EDTA on digitalis induced bigeminal premature beats. *A*) before, *B*) during, *C*) after EDTA infusion.

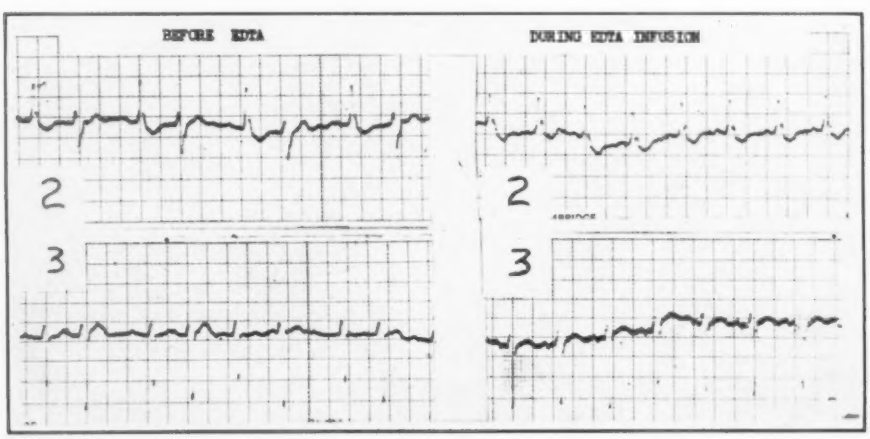

Fig. 3.—Effect of EDTA on digitalis induced arrhythmia.

Six-hundred milligrams of disodium EDTA in 250 ml. 5% glucose in water was given in a half-hour period intravenously. After 60 ml. had been infused in the initial 10 minutes the rhythm converted to regular sinus rhythm with a heart rate of 130 (Fig. 3). The arrhythmia did not recur. Serum calcium, initially 9.6 mg. per 100 ml., fell to 8.5 mg. per 100 ml. after completion of the EDTA infusion.

The patient's clinical condition improved after restoration of sinus rhythm but 12 hours later she was found to be comatose and intravenously until signs of toxicity appeared. There was no evidence of a digitalis effect on the electrocardiogram until 2.4 mg. of Cedilanid had been given. Two hours after 2.8 mg. of Cedilanid had been given the patient became nauseous, vomited, and exhibited nodal bradycardia illustrated in Fig. 4. No further digitalis was given for a period of 16 days. At this time Cedilanid was again given intravenously in a dose of 1.6 mg., but without prior administration of EDTA. Two hours later an electrocardiogram revealed bradycardia and T wave changes indicative of a

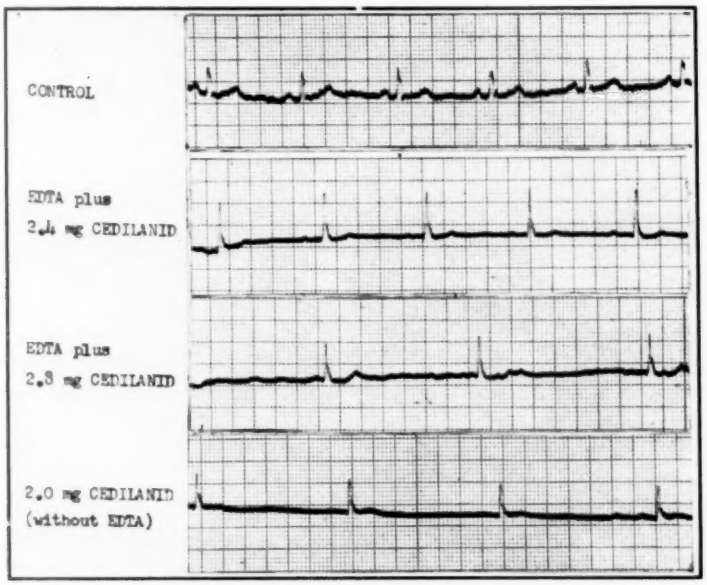

Fig. 4.—Protective effect of EDTA against digitalis toxicity induced by Cedilanid.

expired. There was no sign of tetany at any time after the EDTA infusion until death. Necropsy revealed calcific aortic stenosis, left ventricular hypertrophy, bilateral pleural effusion and infarction of the right middle lobe. Death appeared unrelated to the therapy given.

CASE 4. A woman of 87, who had been hospitalized for custodial care because of cerebral vascular disease and who had no evidence of heart disease, was given 600 mg. of disodium EDTA in 250 ml. 5% glucose in water in a half hour period. Immediately thereafter 1.6 mg. of lanatoside C (Cedilanid) was given intravenously, following which 0.4 mg. of Cedilanid was given every 2 hours digitalis effect. An additional 0.4 mg. of Cedilanid promptly caused nausea, vomiting and nodal bradycardia illustrated in Fig. 4. The total dose of 2.0 mg. produced effects substantially similar to that produced by the almost 50% greater dose of Cedilanid given after priming with EDTA, indicating that administration of EDTA augmented substantially the amount of digitalis required to produce toxicity.

CASE 5. A normal woman of 70, hospitalized for custodial care was given 1.6 mg. of lanatoside C (Cedilanid) intravenously in a single dose. Two hours later successive doses of 1.5 cat units of acetylstrophanthidin were given intravenously at 5-minute intervals

until major electrocardiographic signs of digitalis intoxication appeared (Fig. 5). After the priming dose of lanatoside C slight depression of the ST segment developed, which became marked after 3.0 cat units of acetylstrophanthidin had been given. After 6.0 cat units of acetylstrophanthidin, paroxysmal atrial tachycardia with block and varying configuration of the ventricular complex appeared, following which no further glycoside was given.

mg. per 100 ml. three hours after giving the magnesium EDTA.

Comment. Interrelationships between digitalis, calcium and potassium have long been recognized (Zondek[30]). There is evidence that the effects of digitalis and of calcium on cardiac irritability are mediated by their influence on myocardial cellular permeability to potassium. Digitalis and calcium act, at least in part, at the cellular membrane (Hajdu and Szent-Györgyi[18], and Loewi[20]), influencing ionic permeability. Digitalis reduces myocardial potassium (Hellems, Regan and Talmers[19], and Blackmon *et al.*[3]) and inhibits potassium influx into the myocardium (Conn[8]). It is probable that calcium behaves similarly for in animals in whom acute lowering of ionized serum calcium is produced by

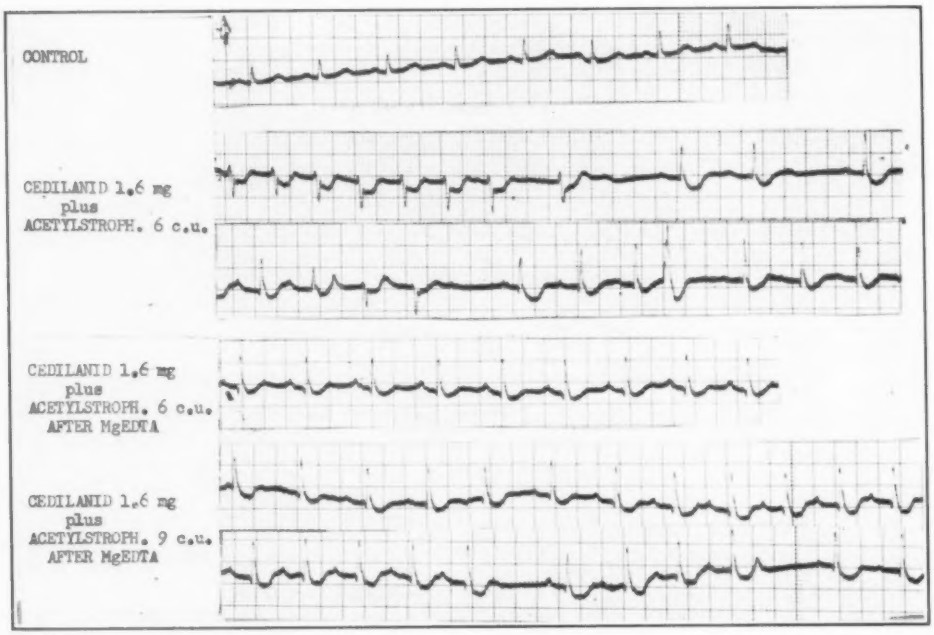

Fig. 5.—Protective effect of magnesium EDTA against digitalis toxicity induced by Cedilanid plus acetylstrophanthidin.

Fourteen days later the patient was given magnesium EDTA intravenously (total magnesium, 44 mg.) followed within 30 minutes by 1.6 mg. of lanatoside C. Two hours later 1.5 cat units of acetylstrophanthidin was given intravenously at 5-minute intervals, as in the control study 2 weeks earlier. Atrial paroxysmal tachycardia with block appeared after 9.0 mg. of acetylstrophanthidin had been given over a 30-minute period. The arrhythmia was less marked than that which had occurred with a smaller dose of acetylstrophanthidin when magnesium EDTA had not been administered (Fig. 5). The serum calcium level, which was 9.8 mg. per 100 ml. fell to 8.9

Na_2 EDTA there is an increased sensitivity of the heart to hyperkalemia (Grumbach, Howard and Merrill[16], and Page and Real[24]). Conversely, calcium induced ventricular arrhythmias do not occur when potassium is administered simultaneously (Grumbach, Howard and Merrill[16]).

It has been well established that digitalis and calcium have a synergistic effect on the heart (Clark[7], Gold and Edwards[13], Loewi[21], and Werschinin[29]). The inotropic action of digitalis depends on the presence of calcium (Clark[7]), and it has been held that the action of digitalis is basically due to a fixation of calcium at the myocardial cell membrane (Loewi[20]). Experimentally calcium alone has effects on rhythmicity and contractility identical with those of digitalis. Clinically the authors have observed a striking therapeutic response in patients with acute pulmonary edema in whom intravenous calcium gluconate was given as the sole therapeutic measure (Gubner and Kallman[17]). Ballistocardiographic studies revealed that the effect of calcium in augmenting the force of the heart beat was more prompt and of greater magnitude than that produced by acetylstrophanthidin.

The foregoing provide a basis for anticipating, since calcium and digitalis have synergistic effects, that lowering of serum calcium might mitigate the toxic effects of digitalis. This proved to be the case. The prompt therapeutic effect observed is to be attributed to the rapid sequestration of ionized serum calcium by ethylenediamine tetraacetic acid. The circulating serum calcium is not actually lowered by EDTA but the fraction bound to the chelating agent is rendered physiologically inert and is not precipitated when serum calcium is estimated. EDTA is excreted in the urine carrying bound calcium, with total excretion within 48 hours (Foreman and Trujillo[12]).

The 600-mg. dose of EDTA employed in the present study is a small one. Three grams may be given safely within a 20-minute period, with no change other than a greater degree of hypocalcemia with accompanying electrocardiographic changes, and transitory fine muscular tremor and acral numbness (Bechtel, White and Estes[2]). Large doses of sodium EDTA (100 mg./kg.) administered rapidly intravenously to rabbits reduce ionized serum calcium precipitously and cause death by hypocalcemic tetany (Popovici *et al.*[25]).

Ethylenediamine tetraacetic acid has been employed clinically principally as a vehicle to promote excretion of heavy metals, as in lead and plutonium poisoning. It has been reported that repeated administration of large doses can produce a temporary toxic nephrosis with hydropic degeneration of the proximal tubules (Foreman, Finnegan and Lushbaugh[11]). This hazard does not apply in the treatment of digitalis intoxication, since in the cases treated in the present study a single small dose proved adequate to restore sinus rhythm. Death occurred in one patient (Case 3) twelve hours after administration of EDTA, but the patient was moribund at the time it was given, and necropsy did not suggest that death was due to any drug toxicity.

Chelation of serum calcium proved effective in abolishing both supraventricular and ventricular arrhythmias induced by digitalis. It has become increasingly recognized that paroxysmal atrial tachycardia with varying block is one of the commoner arrhythmias produced by digitalis. This was present in 3 of the 5 cases studied (Cases 1, 3, 5). This arrhythmia may masquerade as ventricular tachycardia

and ventricular extrasystoles, as illustrated in Figs. 1 and 3, due to partial block in conduction producing a bundle branch block pattern which simulates ectopic ventricular beats.

Cases 1, 2 and 3, in which EDTA was employed therapeutically illustrate an aspect of digitalis toxicity which has not received sufficient emphasis, namely, that digitalis toxicity is hazardous not only because fatal arrhythmias, such as ventricular fibrillation may be induced, but because heart failure may be aggravated greatly by the arrhythmias. This was the situation in Cases 1, 2 and 3, and in all termination of the arrhythmia was accompanied by prompt clinical improvement.

The dose of digitalis required for digitalization and maintenance therapy varies considerably in different people. In addition to body stores of potassium and myocardial potassium content it appears probable that the level of serum calcium may be of importance in determining the response to digitalis.

Summary and Conclusions. 1. Arrhythmias due to digitalis toxicity were terminated promptly in 3 patients by intravenous infusion of the disodium salt of ethylenediamine tetraacetic acid, a chelating agent which binds and inactivates serum calcium. In 2 other patients prior administration of Na_2 EDTA in one, and the magnesium salt of EDTA in another, significantly increased the dose of digitalis glycosides required to produce major arrhythmias.

2. The use of EDTA in the treatment of digitalis toxicity is predicated on the synergistic relationship between digitalis and calcium. It appears probable that their effects on cardiac rhythmicity are mediated via their action at the myocardial cell membrane, determining permeability to potassium. Digitalis and calcium promote potassium loss from the myocardium thereby increasing irritability.

3. The use of EDTA offers certain advantages over potassium administration in treating digitalis toxicity. Its action is very prompt and is safer than intravenous potassium. Oral potassium is slow in effect and large doses are required which may not be well tolerated.

4. EDTA is effective in abolishing both atrial and ventricular ectopic rhythms caused by digitalis. In certain instances atrial arrhythmias produced by digitalis may mimic ventricular extrasystoles and ventricular tachycardia due to accompanying functional bundle branch block.

5. It is important that arrhythmias due to digitalis toxicity be controlled promptly in patients with heart failure, for apart from the classic hazard of ventricular fibrillation, heart failure may be paradoxically aggravated by digitalis when arrhythmias are produced by overdosage.

ADDENDUM. The effect of EDTA on ectopic beats is not limited to those caused by digitalis toxicity. In a nondigitalized male of 29 in heart failure with atrial fibrillation, who had persistent short bursts of successive ectopic ventricular beats and bigemini, the extrasystoles disappeared during EDTA infusion and did not recur for several hours. Intravenous KCl (7½ mEq.) also abolished the ectopic beats. Fractional 0.1 gm. doses of calcium gluconate given immediately after 15 mEq. of KCl caused a return of extrasystoles after 0.2 gm., with bigemini after 1.0 gm., which was controlled by a further 5 mEq. of KCl. These observations indicate a close inverse relationship between the effects of calcium and potassium on cardiac rhythmicity.

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SUMMARIO IN INTERLINGUA

Tractamento de Toxicitate a Digitalis per Chelatation de Calcium del Sero

1. Arrhythmias debite a toxicitate per digitalis esseva terminate promptemente in 3 patientes per infusion intravenose del sal binatrial de acido ethylenediaminetetraacetic (AEDT) que es un agente chelatante capace a ligar e a inactivar calcium del sero. In 2 altere patientes, le previe administration de Na_2AEDT (in un) e del sal magnesial de AEDT (in le altere) augmentava significativemente le dose de glycosidos de digitales requirite pro le production de major arrhythmias.

2. Le uso de AEDT in le tractamento de toxicitate a digitalis es conditionate per le relation synenergic inter digitalis e calcium. Il pare probabile que le effectos de digitalis e de calcium super le rhythmo cardiac es mediate per lor action al membranas cellular myocardial ubi illos determina le permeabilitate pro kalium. Digitalis e calcium promove le perdita de kalium ab le myocardio e assi augmenta su irritabilitate.

3. Le uso de AEDT ha certe avantages super le administration de kalium in le tractamento de toxicitate per digitalis. Su action es multo prompte, e illo es plus secur que kalium intravenose. Kalium oral es lente in su action e debe esser administrate in grande doses que non es semper ben tolerate.

4. AEDT es efficace in eliminar rhythmos ectopic tanto atrial como etiam ventricular que ha essite causate per digitalis. In certe casos, arrhythmias atrial producite per digitalis pote simular extrasystoles ventricular e tachycardia ventricular del typo causate per accompaniante bloco de branca functional.

5. Il es importante que arrhythmias causate per toxicitate a digitalis es subjugate promptemente in patientes con disfallimento cardiac, proque, a parte le hasardo classic de fibrillation ventricular, disfallimento cardiac pote esser aggravate paradoxemente per digitalis quando doses excessive de illo resulta in arrhythmias.

SUMMARIO IN INTERLINGUA

(See page 129 for original article)

Le Effecto de Infarcimento Myocardial Super le Dimensiones del Corde

Un studio subsequential de roentgenologia esseva facite in 489 patientes qui superviveva acute infarcimento myocardial pro al minus 2 menses e qui habeva cordes de dimensiones normal al tempore del infarcimento. Esseva includite solmente patientes qui se habeva restablite ab lor (supponitemente) prime infarcimento.

Le majoritate del patientes esseva sub observation durante inter 1 e 10 annos.

Duo pro cento (8 casos) disveloppava hypertrophia cardiac in le absentia de generalmente acceptate factores del typo de hypertension, morbo de valvula cardiac, o corde pulmonal.

Allargamento cardiac esseva primo notate a periodos de inter 6 menses e 13 annos post le declaration del infarcimento.

Omne le 8 patientes qui disveloppava hypertrophia cardiac habeva associate disfallimento cardiac congestive.

Multiple infarcimentos myocardial non causava hypertrophia cardiac in le absentia de disfallimento congestive.

Es exprimite le opinion que hypertrophia cardiac se disveloppa con disfallimento congestive que de su parte resulta ab un aneurysmo myocardial o extense fibrosis myocardial o ambe iste complicationes del infarcimento myocardial.

EFFECT OF L-GLUTAMIC ACID ON METABOLISM OF PATIENTS WITH HEPATIC ENCEPHALOPATHY*

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Elevation of the blood ammonia level is considered to be the most probable major cause of the encephalopathy accompanying advanced hepatic insufficiency. Pavlov[5], in 1893, demonstrated a relationship between hepatic encephalopathy and protein consumption in dogs with portacaval anastomoses. As early as 1932 (Van Caulaert and Deviller[14]), it was noted that patients with cirrhosis may become comatose following ammonium chloride administration. McDermott and Adams[8] have recently reported reversible neurological deficits occurring in patients with portacaval shunt after the ingestion of nitrogenous substances. Although there has not been demonstrated a quantitative relationship between the degree of cerebral dysfunction and of elevation of blood ammonia values in hepatic encephalopathy, nevertheless, attempts have been made to reduce blood ammonia levels in this condition by the administration of l-glutamic acid. In the first of these attempts, Walshe[15], in 1953, noted a reduction of blood ammonia levels and believed that there was a favorable clinical response. Others have subsequently reported varying results as to the therapeutic effectiveness of this amino acid in hepatic encephalopathy (Eiseman, Bakewell and Clark[2], and McDermott, Wareham, and Riddell[9]).

Previous studies (Fazekas, Ticktin and Alman[3]) have demonstrated a reduction of total cerebral oxygen consumption in patients with hepatic coma. In the present report the effects of the administration of l-glutamic acid on cerebral oxygen consumption, blood ammonia levels, and electroencephalograms of patients with varying degrees of cerebral dysfunction due to hepatic insufficiency are presented. In addition, cerebral findings are reported on 3 patients who recovered spontaneously from hepatic encephalopathy.

Method. Ten patients were studied, and in all cases there was clinical and laboratory evidence of severe endogenous hepatic insuf-

*This investigation was supported by a research grant (PHS B–178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

ficiency, the result of advanced cirrhosis. There were varying degrees of cerebral dysfunction, stupor, or coma at the time these studies were undertaken. Cerebral blood flow, oxygen consumption, and cerebral arteriovenous ammonia differences were determined in all subjects at the beginning of the study. In three subjects who recovered spontaneously from their hepatic encephalopathy, cerebral studies were then repeated. In 7 subjects, monosodium l-glutamate was administered intravenously in amounts ranging from 16 to a total of 150 gm. over a period of one to 3 days. In 4 of the above 7 subjects, electroencephalograms were obtained prior to and during the administration of monosodium l-glutamate. Blood ammonia determinations were repeated at varying intervals while subjects were receiving l-glutamate intravenously. The amino acid was dissolved in 5% dextrose in water in a concentration of 50 mg. per 1000 ml.

Scheinberg and Stead's modification[12] of Kety and Schmidt's procedure[6] for the determination of cerebral blood flow was applied in this study. The oxygen content of the blood was determined by the manometric technique of Van Slyke and Neill[11]. Mean arterial pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer (Alman and Fazekas[1]). Blood ammonia levels were determined by a microdiffusion nesslerization method modified from Seligson[13] on freshly drawn blood from the femoral artery and the jugular bulb. Blood was drawn without stasis into a previously calibrated 2 ml. syringe, and 1 ml. specimens were injected into each of 2 Seligson microdiffusion vessels within 15 to 45 seconds after withdrawal. In all cases a water blank was run with each pair of arterial and venous samples. Electroencephalograms were recorded on a 6-channel Grass electroencephalograph in the conventional manner.

Results. Table 1 presents the cerebral findings in 3 subjects who made a spontaneous recovery from hepatic coma. In all of these individuals there was an increase in cerebral blood flow observed after recovery, apparently related to an increase of mean arterial pressure; cerebral vascular resistance showed no appreciable change. The cerebral metabolic rate rose in 2 subjects after spontaneous recovery, but remained essentially unchanged in one patient.

TABLE 1.—CEREBRAL VALUES IN PATIENTS RECOVERING SPONTANEOUSLY FROM HEPATIC COMA*

	CBF		*$CMRO_2$*		*CVR*		*MAP*		*Arterial NH_3*		*Venous NH_3*	
Age	*C*	*R*	*C*	*R*	*C*	*R*	*C*	*R*	*C*	*R*	*C*	*R*
55	37.6	52.7	1.4	2.0	1.7	1.8	62	95	2.3	1.2	2.1	1.1
34	108.9	127.6	1.8	1.7	0.7	0.6	72	82	1.5	0.7	1.6	0.6
60	29.5	44.1	1.1	2.1	1.6	1.5	47	67	2.4	1.7	2.1	1.4

*CBF signifies cerebral blood flow in ml./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in ml./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/ml. blood/100 gm. of brain/min.; MAP, mean arterial blood pressure in mm. of Hg; C, coma; R, recovery.

The arterial ammonia levels were associated with recovery from hepatic coma although these values remained somewhat elevated above normal in 2 cases. The cerebral venous ammonia level changes followed the arterial values with the usual slight further reduction due to cerebral ammonia uptake.

Table 2 presents the average values of cerebral measurements (26 observations) in 7 patients taken before (13 observations) and at intervals (13 observations) during the intravenous infusion of sodium l-glutamate. In none of these cases was there any demon-

strable clinical effect. There was no significant change in any of the cerebral measurements nor in electroencephalograms performed in 4 of these subjects.

In Table 3 are shown the arterial and cerebral venous ammonia levels before and after the administration of varying amounts of sodium l-glutamate over different time intervals. A significant reduction in arterial and cerebral venous ammonia levels was demonstrated in 6 subjects who received from 16 to 40 gm. of the amino acid over periods of 1.5 to 6 hours. In 3 of these subjects, in whom the infusion was continued for 15 to 30 hours, the ammonia values tended to return to, or above, the preinfusion values. A fourth subject who received a prolonged infusion showed an appreciable reduction in blood ammonia. In 2 subjects whose infusions were continued for 3 days the arterial and venous am-

TABLE 2.—MEAN CEREBRAL VALUES BEFORE AND DURING ADMINISTRATION OF SODIUM L-GLUTAMATE*

	CBF		*$CMRO_2$*		*CVR*		*MAP*		*Total Glutamate*
Age	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*(gm.)*
60	32.0	31.8	1.2	1.2	1.4	1.6	45	48	24
48	25.5	35.0	1.6	1.7	2.0	1.7	52	57	64
42	59.5	63.3	1.7	1.0	0.8	0.8	50	51	20
53	36.2	38.3	1.4	2.6	1.8	1.3	62	51	48
49	54.4	43.3	1.9	1.8	1.0	1.2	51	47	40
46	39.2	22.1	1.4	1.8	1.7	1.7	65	55	30
52	48.9	60.8	1.7	1.8	2.0	1.5	94	93	50
				Mean Values†					
50	42.2	42.1	1.6	1.7	1.5	1.4	60	57	39

*CBF signifies cerebral blood flow in ml./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in ml./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/ml. blood/100 gm. of brain/min; MAP, mean arterial blood pressure in mm. of Hg; C, average values before administration of glutamate; E, average values during administration of glutamate.

†Differences in mean values not significant.

TABLE 3.—MEAN CEREBRAL ARTERIAL AND VENOUS AMMONIA VALUES BEFORE AND AFTER ADMINISTRATION OF SODIUM L-GLUTAMATE

	Arterial NH_3				*Venous NH_3*			
Age	*Control*	*After 1½–6 hrs. 16–40 gm.*	*After 15–30 hrs. 20–50 gm.*	*After 3 days 64–150 gm.*	*Control*	*After 1½–6 hrs. 16–40 gm.*	*After 15–30 hrs. 20–50 gm.*	*After 3 days 64–150 gm.*
60	2.3	1.7	2.6		2.1	1.5	2.2	
48	2.3	1.7	2.0	3.9	1.5	1.3	1.6	3.8
42	2.8		1.0		2.6		0.7	
53	2.6	2.0			2.2	1.8	0.8	
49	1.2	0.5			1.0	0.3		
46	1.4	1.0			1.3	0.7		
52	4.2	2.9	3.6	3.8	3.7	2.3	3.1	3.6
				Mean Values				
50	2.4	1.6*	2.3	3.8	2.1	1.3*	1.7	3.7

*Significant difference, $p < .05$

monia values rose to, or above, preinfusion levels. In all cases there was the usual small difference between arterial and cerebral venous ammonia levels due to cerebral ammonia uptake.

Discussion. The uniformly low rate of total cerebral oxygen consumption in patients with hepatic encephalopathy has previously been noted (Fazekas, Ticktin and Alman[3]) and suggests that the clinical disorder reflects a disturbance in oxidative metabolism. As demonstrated in the 3 subjects of this study who recovered spontaneously from their encephalopathy, improvement may be associated with an increase in cerebral oxygen consumption although this function usually continued to be somewhat depressed. It would seem reasonable, therefore, that if sodium l-glutamate was therapeutically effective, it should correct the oxidative defect in hepatic encephalopathy, and an increase in cerebral oxygen consumption would be apparent following its administration.

It is, therefore, important to examine the possible reasons for failure of sodium glutamate to produce clinical or otherwise measurable improvements in the subjects of this study. The most obvious of these reasons is failure of sodium l-glutamate to penetrate the blood brain barrier. It has been demonstrated in mice and rats that after glutamate administration there is no significant increase in brain glutamic acid despite considerable uptake by liver and muscle (Friedberg and Greenberg[4], and Klein and Olsen[7]). Therefore, any therapeutic effectiveness of glutamate administration would have to depend upon its peripheral metabolic effects.

In our subjects, the administration of l-glutamate even when continued for as long as 3 days, failed to sustain the initial reduction in blood ammonia levels. It must be noted that the reduction in blood ammonia, although initially consistent and significant, was relatively small, and the lowest levels achieved were in most instances still above normal values. This observation may perhaps explain the consistent therapeutic failure of sodium l-glutamate. The fact that there is no demonstrable correlation between degree of central nervous system depression and quantitative values of elevated blood ammonia was somewhat disturbing, but it should be pointed out that in coma resulting from hypoglycemia, diabetes, or uremia, there is also no quantitative correlation between the level of the abnormal blood constituents and the degree of central nervous system depression.

The finding that blood ammonia tended to rise in spite of continued l-glutamate administration supplements the observation of McDermott, Wareham and Riddell[9] who noted a similar rebound following termination of glutamate infusion. It is probable that the initial reduction of ammonia was due to combination with glutamate to form glutamine in liver and muscle, but that this mechanism (ammonia + glutamic acid + adenosinetriphosphate and magnesium = glutamine), in spite of ready availability of excess amounts of ammonia and glutamate, becomes saturated or exhausted.

Although as previously noted, there is general agreement that increased blood ammonia levels may be a precipitating cause of hepatic encephalopathy, there remains some doubt as to whether there is a different, although associated, metabolic defect, which is not affected by manipulation of ammonia metabolism. For example, Walshe[15] showed that certain other substances, particularly methionine, may be of fundamental etiology. In such instances, even if it were possible to reduce blood ammonia levels to normal

values, there might well be no clinical or otherwise measurable response. In our subjects, even if exogenous glutamate had been successful in producing satisfactory reduction of blood ammonia levels, the possibility remains that the neurological metabolic disturbance observed may have already reached an irreversible state, although this seems most unlikely.

The interference with oxidative metabolism observed in the brain in the presence of high blood ammonia levels may also be present in liver and muscle. Since adenosinetriphosphate, which is essential for the synthesis of glutamine (from ammonia and glutamic acid), itself depends upon oxidative mechanisms for its formation, there may well be an adenosinetriphosphate deficiency in subjects with high blood ammonia levels which is primarily responsible for the shortness of duration of ammonia reduction during glutamate administration. This possibility was explored clinically by Pelner[10] who described excellent results following administration of adenosine-5-monophosphate in two cardiac subjects with ammonium encephalopathy and one patient with hepatic coma. To our knowledge, the effect of adenosine-5-monophosphate administration, with or without concurrent sodium l-glutamate, upon blood ammonia levels has not been determined.

Summary and Conclusions. The administration of sodium l-glutamate, even when continued for prolonged periods in patients with hepatic coma, had only a temporary effect in reducing the elevated blood ammonia levels and produced no apparent changes in clinical status, cerebral oxygen consumption, or electroencephalograms. Despite its continued administration, blood ammonia levels rose to, and even above, preinfusion values. It is postulated that exogenous sodium glutamate may saturate or exhaust an impaired glutamine synthesis mechanism in patients with hepatic coma. Unless an effective means of producing physiologically important reduction of elevated blood ammonia levels is found, the relative importance of this ion in hepatic encephalopathy remains obscure.

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(Interlingua on page 154)

AN EFFECTIVE COMBINATION IN THE TREATMENT OF THE HYPERTENSIVE PATIENT

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The recent introduction of a variety of agents for the management of the hypertensive patient has made it increasingly difficult to select the drug or drugs most efficacious. Even more difficult is the day-to-day care of such patients because effective therapy is predicated on individualizing the dosage regimen with painstaking devotion to dosage titration and correction of untoward side effects.

Extensive studies with a host of therapeutic agents in more than 400 patients during the past 4 years indicated that mecamylamine offered certain advantages over existing ganglion-blocking agents and that the addition of meprobamate to the dosage regimen was highly desirable especially in emotionally labile patients with moderate to severe hypertension.

Mecamylamine, a secondary amine, is the first effective autonomic ganglion-blocking agent in clinical use which is not a quarternary ammonium compound. Its major advantage is that it is completely absorbed from the gastrointestinal tract. Erratic absorption with marked fluctuations in blood pressure, so typical of the quarternary ammonium compounds, is less frequently observed during therapy with mecamylamine. Moreover, its duration of action is longer than other ganglion-blocking agents (Ford and Moyer[2], and Stone *et al.*[4]).

Meprobamate was selected because extensive studies (Borrus[1] and Selling[3]) have shown it to be a helpful sedative and soporific for anxiety and tension without the recognized limitations of phenobarbital and reserpine. Reserpine is also helpful for adjunctive therapy, but the threat of psychic disturbances, water retention, increased weight gain, and persistent nasal stuffiness have caused us to largely abandon it for meprobamate. Absence of such major toxic effects make meprobamate a preferred drug for adjunctive treatment of anxiety which usually accompanies the hypertensive cardiac patient.

The use of meprobamate in combination with mecamylamine has been highly effective. While the study has shown that meprobamate alone has little, if any, hypotensive action, potentiation of the action of mecamylamine by meprobamate was evident in some patients. Moreover, subjective response

was usually greater with the combination than with either drug alone.

Methods and Materials. This study consisted of a group of 37 patients with moderate to severe hypertension treated on an outpatient basis in the Cardiac Clinic of the St. Barnabas Medical Center, Newark, New Jersey, and in the authors' private practice. Severity index, according to the criteria of Duncan, was at least Grade II in all patients. Controls were established by taking the average of a minimum of 6 separate blood pressure and pulse rate determinations in the supine and upright positions.

During therapy patients were observed at least once weekly and, in many instances, daily. Pressures were taken in both the supine and upright positions. Duration of follow-up was 14 months with mecamylamine alone, 2 months with meprobamate alone, and 6 months with meprobamate in combination with mecamylamine.

All patients were carefully evaluated prior to therapy. Complete history and physical examination, complete blood count, electrocardiogram, chest roentgenograms, urinalysis, serology, and blood urea nitrogen determinations were made. Each week a brief history and physical examination were performed. Blood pressure in both standing and sitting positions, pulse rate determination, and weight were also taken at every visit.

Of the 37 patients treated, 26 were females and 11 males. Their ages ranged from 30 to 70 with 2 in the 30 to 40 age group, 9 in the 40 to 50 group, 12 in the 50 to 60 group and 14 in the group above the age of 60. Only one patient had previously diagnosed myocardial infarct. Diabetes mellitus was present as a complication in one other patient. All the patients were on low salt diets. Many of the patients were also receiving digitalis and chlormerodrin for coexisting decompensation.

Initial dosage of mecamylamine was 2.5 mg. three times daily after meals. In our experience this dose never produced hypotension and was inadequate. Dosage of mecamylamine had to be gradually increased each week until an adequate reduction in blood pressure was elicited or side effects became extremly troublesome. The majority of our patients required at least 10 mg. per day of mecamylamine, 4 patients required 60 mg. per day, 2 required 75 mg. per day, and one needed 90 mg. per day before satisfactory response was obtained. Initially 400 mg. of meprobamate were given twice daily. This was later increased to 400 q.i.d. No higher levels were needed.

Constipation proved to be the most common side effect with almost all patients (29) complaining of it at some stage of the therapy. Constipation proved to be a relatively good sign of ganglion-blocking because reductions in blood pressure frequently occurred simultaneously.

Epigastric discomfort occurred in 7 of the patients, and could usually be relieved by slight reduction of mecamylamine dosage. Six patients complained of vertigo, which was generally relieved by bed rest or sitting down or slight reduction of mecamylamine dosage. Headaches, a major complaint prior to treatment in 95% of the patients, persisted in only 4 during therapy. Urinary retention of a transient nature occurred in 3 patients; impotency in one.

Results. Using as the criterion for response a reduction in the mean blood pressure of 20 mm. Hg or more or a return to normotensive levels, the over-all response rate to combination therapy of mecamylamine and meprobamate was 95%. During the long course of therapy with mecamylamine alone 28 of 37 patients showed a significant response.

Meprobamate alone did not significantly alter the blood pressure in any patients in the series. Four patients experienced a reduction of up to 10 mm. in their diastolic pressures, but the effect was transient and could have been caused by a temporary reduction of environmental stresses.

The addition of meprobamate facilitated management and provided the patient with a greater sense of well-being. In many instances the patients stated that they had seldom felt better and it was evident to the examining physician that the basic concern of most hypertensives had been considerably allayed.

Illustrative Case Reports. CASE 1. G.W., a 57-year-old colored male with a cardiac diagnosis of arteriosclerotic heart disease, aortic sclerosis, coronary insufficiency, and with electrocardiographic evidence of myocardial

damage, was placed on mecamylamine alone in July, 1955. A starting dose of 2.0 mg. four times a day was employed. The blood pressure remained at 190/130 in spite of an increase in dosage to 5.0 mg. four times a day. The blood pressure readings were recorded as 190/130, 190/140, 180/130, 170/120, 180/120. Mecamylamine was discontinued and the blood pressure rose to 200/150, 210/160. The patient was then placed on mecamylamine 5.0 mg. and meprobamate 400 mg. three times a day. There was a drop in blood pressure to 170/130 but a subsequent rise to 190/140 upon again discontinuing the drugs because he ran out of them. Under medication patient commented that he felt fine and that his appetite was better than ever. There was no constipation and no urinary difficulty. Upon increasing the dosage of mecamylamine to 10 mg. three times a day, the patient complained of vertigo, constipation, and difficulty in initiating the urinary stream. But, in spite of this, his comment was that he was "feeling extremely well." The blood pressure had dropped to 160/90 and maintained at this level.

CASE 2. F.W., a 52-year-old white female with a cardiac diagnosis of arteriosclerotic and hypertensive heart disease. The patient's blood pressure before treatment varied from 200/100 to 180/110. The patient was placed on mecamylamine 2.5 mg. and meprobamate 400 mg. three times a day. The blood pressure remained at 180/100, 170/100 and up to 240/120. But the patient reported that she felt better than before, and has no complaints. There was a nonspecific feeling of well-being. The dosage was increased to mecamylamine 10 mg. and meprobamate 400 mg., four times a day with a drop in pressure to 130/90 and with continued feeling of well-being.

CASE 3. A.J., a 41-year-old colored female with essential hypertension. A thoracolumbar sympathectomy had been performed in 1953 with poor result both as to blood pressure level and as to relief of the prime complaint, headache. Through the year the patient had been unsuccessfully managed with rauwolfia extracts, pentolinium, sedation, hexamethonium, pentaerythritol, chlorpromazine and combinations of these drugs. Tests were performed to rule out pheochromocytoma. The blood pressure readings ranged about 200/140, 210/130, 190/120, 240/140, 180/136. Of greatest importance to the patient was the severity and unremitting character of the headache. In October, 1956, meprobamate and mecamylamine were instituted in dosage of 400 mg. and 5.0 mg. t.i.d. respectively. The headache was better, but still present. The dosage of mecamylamine was progressively increased to 10 mg. t.i.d. but the patient developed weakness and vertigo and on her own discontinued medication. However, after 4 days, the headache was so bad she returned to the meprobamate and mecamylamine and felt better again. The difference is so pronounced that the patient would rather have the lightheadedness of a full therapeutic effect of the medication than the severe headache which she has suffered for years. The blood pressure now ranges from 130/96 to 160/120 on dosage from meprobamate 400 mg. q.i.d. and mecamylamine 15 mg. q 2 hours, to meprobamate 400 mg. q.i.d. and mecamylamine 10 mg. q.i.d.

CASE 4. A.C., a 38-year-old white man complained of loss of vision for 3 weeks. He awakened one morning and could not read the paper clearly; noticed double vision and scotomata. He had had hypertension and albuminuria for 7 years. He was treated with reserpine, hexamethonium, pentolinium and phenobarbital; his initial blood pressure was 240/130; fundi Grade III. After three months of above therapy, blood pressure was 210/120. There was a slight improvement of vision but fundi improved only slightly. Inversine started at 5 mg. t.i.d. for one month with no change at all in objective or subjective findings. Dose increased to 25 mg. daily the next month with no change in clinical picture. In the past 4 weeks, the dose was increased to 15 mg. every 2 to 3 hours. There was some dizziness upon standing which improved after he was up for a while. Last blood pressure systolic 170 to 190 and diastolic 90 to 108. Patient much improved and fundi now Grade I–II. Maintenance dose now 15 mg. q.i.d.

Discussion. It is too early to predict how this treatment will modify the course of hypertensive heart disease. It is enough to state that: significant reductions in both systolic and diastolic blood pressures occurred in most patients; those individuals who exhibited changes in optic fundi were often improved during the course of therapy; marked relief of headaches and apprehension were evident in almost every patient.

It became evident in this study that it was possible to achieve an adequate hypotensive response of at least 20 mm. Hg in almost every patient if sufficient care was exercised to individualize the dosage by careful titration to high levels. Such high levels (as much as 90 mg. per day) always produced some manifestation of the side action of the drug such as lightheadedness and constipation. While this must be considered clinically a toxic reaction, high dosage levels (at least 40 mg. per day) must be attained before adequate response is reached. Despite such side reactions, the addition of meprobamate usually created a more cooperative patient with fewer complaints.

The physician, therefore, must be acquainted with the pharmacodynamics of these drugs in order to adequately treat hypertensive individuals. Inadequate titration of dosage leads to failure with most patients and loss of confidence in the therapeutic effects of the drugs.

Side effects are difficult to avoid during hypotensive therapy, but the serious consequences resulting from them can be circumvented by understanding the modes of action of the drugs.

In the present series of cases it was observed that the dosage level of mecamylamine was somewhat higher than previously reported by other investigators (Ford and Moyer[2]). Most of the patients were on relatively small dosages (2.5 mg. to 5.0 mg.) for many months before it became apparent that much larger doses would be needed. This prolonged period of medication undoubtedly produced a tolerance for the drug which would have been obviated if we had first withheld it for several weeks before increasing dosage.

While no renal insufficiency due to the hypotensive effect of the drug was evident in this series, caution must be observed since this is always a potential danger, especially in hypertensive vascular disease where there may be pre-existing renal insufficiency.

Summary and Conclusions. Thirty-seven patients with hypertensive disease were treated for a period of 17 months with the aid of mecamylamine and meprobamate, singly and in combination.

Twenty-eight of 37 patients with moderately severe and severe hypertension treated with mecamylamine had successful control of blood pressure.

Meprobamate alone had no effect on the blood pressure of the same group.

In combination, meprobamate and mecamylamine provided objective and subjective improvement in 35 of 37 patients. While significant additional reduction in blood pressure did not occur with meprobamate, management of the patients was facilitated considerably. A general sense of well-being, loss of many chronic complaints of a mild nature, and loss of apprehension were all evident in the majority of patients.

Meprobamate has distinct advantages over phenobarbital and reserpine for adjunctive therapy since it has none of the habituating liabilities of phenobarbital and is free of the threat of severe mental depression, water retention and nasal stuffiness of reserpine.

ACKNOWLEDGMENT: Mecamylamine (Inversine) was kindly furnished by Dr. John Beem of Merck Sharp & Dohme Research Laboratories.

Meprobamate (Miltown) was kindly furnished by Dr. Frank Berger of Wallace Laboratories.

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SUMMARIO IN INTERLINGUA

Un Combination Efficace in le Tractamento del Patiente Hypertensive

Trenta-septe patientes con morbo hypertensive esseva tractate durante un periodo de 17 menses per medio de mecamylamino e de meprobamato, individualmente e in combination.

Vinti-octo del 37 patientes con hypertension de grados moderatemente sever o sever attingeva un bon regulation del pression sanguinee sub le regime de mecamylamino.

Meprobamato sol habeva nulle effecto super le pression sanguinee del mesme gruppo.

In combination, meprobamato e mecamylamino provideva melioration objective e subjective in 35 ex 37 casos. Ben que le addition de meprobamato non resultava in significative grados supplementari del reduction in le pression sanguinee, le tractamento del patientes esseva considerabilemente facilitate. Un senso de ben-esser general, le disparition de multe gravamines chronic de natura minor, e le perdita de apprehension esseva omnes evidente in le majoritate del patientes.

Meprobamato ha distincte avantages in comparation con phenobarbital e reserpina como agente de therapia adjunctive, proque illo non ha le propension habituatori de phenobarbital e non presenta le risco de sever depression mental, de retention de aqua, e de constipation nasal que es characteristic de reserpina.

SUMMARIO IN INTERLINGUA

(See page 145 for original article)

Effecto de Acido L-Glutamic Super le Metabolismo de Patientes con Encephalopathia Hepatic

Le administration de l-glutamato de natrium a patientes con coma hepatic, mesmo si continuate durante prolongate periodos de tempore, habeva solmente temporarimente le effecto de reducer le elevate nivello sanguinee de ammoniaco e produceva nulle apparente alterationes in stato clinic, consumption cerebral de oxygeno, o signos electroencephalográphic. In despecto del continue administration del composito, le nivellos sanguinee de ammoniaco montava al valores preinfusional e mesmo superpassava los. Es postulate que exogene glutamato de natrium pote saturar o exhaurir un defecte mechanismo de synthese de glutamina in patientes con coma hepatic. Usque un efficace medio es discoperite pro effectuar un physiologicamente importante reduction de elevate nivellos sanguinee de ammoniaco, le relative signification de iste ion in encephalopathia hepatic debe remaner obscur.

VASCULAR REACTIONS IN ORTHOSTATIC HYPOTENSION: OBSERVATIONS WITH THE HYDROGENATED ERGOT ALKALOIDS

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The present study was carried out to determine the significance of the digital vasoconstrictive reflexes in patients with orthostatic hypotension which was due to a variety of causes. It is believed that these reactions are of diagnostic assistance in identifying the cause of the hypotension.

Method and Material. Cardiovascular reactions were studied using the hydrogenated ergot alkaloids (Hydergine†) as a diagnostic tool. These alkaloids have a central and peripheral action and represent an equal mixture of dihydroergocornine, dihydroergocristine and dihydroergokryptine, and were made available in ampuls, each ml. containing 0.3 mg. The hydrogenated ergot alkaloids have a depressor effect on the vasomotor center and are capable of producing a transient lowering of the arterial pressure after intramuscular or intravenous administration (Winsor[10]). Cardiovascular reactions were studied as controls in 10 normal subjects. In addition 10 patients without elevated arterial pressures were studied before and after the hydrogenated ergot alkaloids, 0.3 mg. by intramuscular injection. An additional patient was studied with advanced cerebral atrophy; one patient was studied after a thoracolumbar sympathectomy; one had pooling of blood in the lower extremities due to severe varicose veins; one had poor muscle tone due to myasthenia gravis and one had a low blood volume following gastric hemorrhage. Studies were made of the blood pressure and pulse rate in the supine and standing positions by auscultation with a mercury manometer. The mean pressure was determined by dividing the sum of the systolic and diastolic pressure by two. Venous pressures in the antecubital vein were studied with the patient standing, with the antecubital vein placed 10 cm. above the 4th intercostal space anteriorly. The transverse diameter of the heart was measured from the Roentgen kymogram. The digital vasoconstrictive reactions to an electric shock were studied plethysmographically with an electronic plethysmograph, with the patient supine. The blood volume was determined using Evans blue dye.

Results. NORMAL SUBJECTS. Digital vascular reflexes to pain were present in all subjects in the fingers and toes. The blood volume was within ±12% of the mean estimated volume. On standing (Table 1) the average systolic and diastolic blood pressures rose slightly with a minimal increase in mean arterial pressure. The average pulse rate increased slightly. The venous pressure did not fall with quiet standing for 15 minutes. The diastolic transverse diameter of the heart did not change after standing for 15 minutes. With the subjects again supine nitroglycerin caused cardiac acceleration and levarterenol caused slowing of the cardiac rate.

HYDROGENATED ERGOT ALKALOIDS. After the drug the vascular reactions to pain in the supine position were absent in the fingers and toes (Fig. 1). The blood volume was normal. About 20 minutes after the injection the patients stood. The systolic pressure fell more than the diastolic pressure. The

*These studies were carried out with a grant from the Los Angeles County Heart Association aided in part by a donation from Mr. Henry Guidera. Technical assistance by Grayce Fleming.

†Hydergine, furnished by Harry Althouse of Sandoz, Inc.

mean pressure fell significantly (Table 1). The cardiac rate did not accelerate. Venous pressure fell 40 mm. of water on standing 3 minutes at which time the patients felt faint and were returned to the reclining position. The diastolic heart size decreased on standing (Fig. 2). With the subjects supine nitroglycerin produced no cardiac acceleration and levarterenol produced no cardiac slowing. The probable mechanism of the absence of cardiac slowing after the hydrogenated ergot alkaloids is shown in Fig. 3.

TABLE 1.—REACTIVITY OF CARDIOVASCULAR SYSTEM IN NORMAL SUBJECTS AND IN PATIENTS WITH ORTHOSTATIC HYPOTENSION

	A	*B*	*C*	*D*	*E*	*F*
	Normal	*Hydrogenated Ergot Alkaloids*	*Brain Disease*	*Thoracolumbar Sympathectomy*	*Varicose Veins and Myasthenia Gravis*	*Bleeding Peptic Ulcer*
Vasoconstrictive reflex at the toe with a painful stimulus	Present	Absent	Absent	Absent	Present	Present
Blood volume compared with normal	0	0	0	0	0	—
Change in mean blood pressure on standing compared with supine	+	—	—	—	—	—
Change in heart rate on standing	+	0	0	+++	+++	+++

+ = an increase
0 = no change
— = a decrease
Graded from 1 to 3 plus

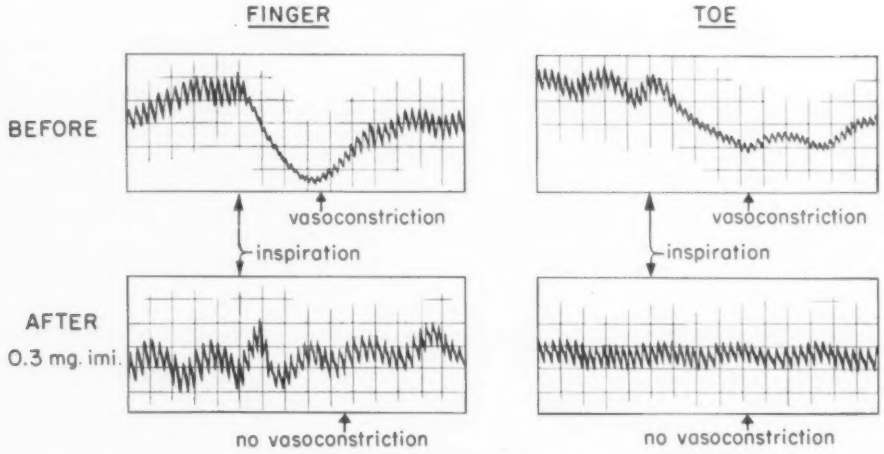

Fig. 1.—Vascular reactions to a painful stimulus before and after the hydrogenated ergot alkaloids.

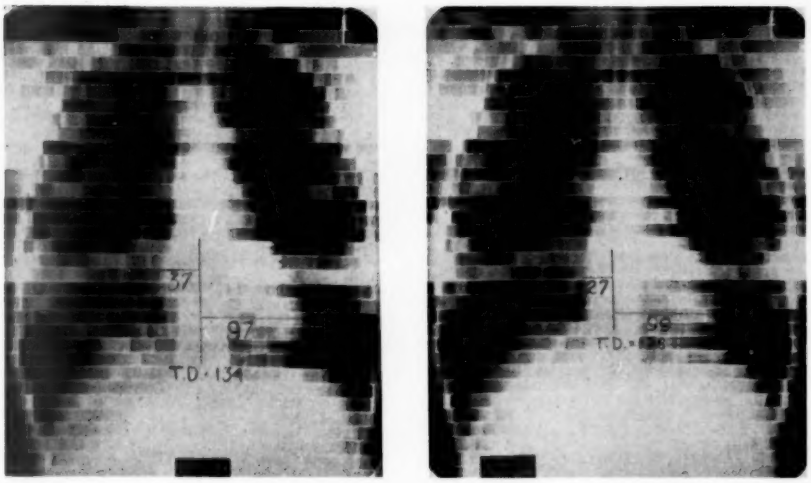

Fig. 2.—Systolic and diastolic heart size before and after the hydrogenated ergot alkaloids in a subject standing.

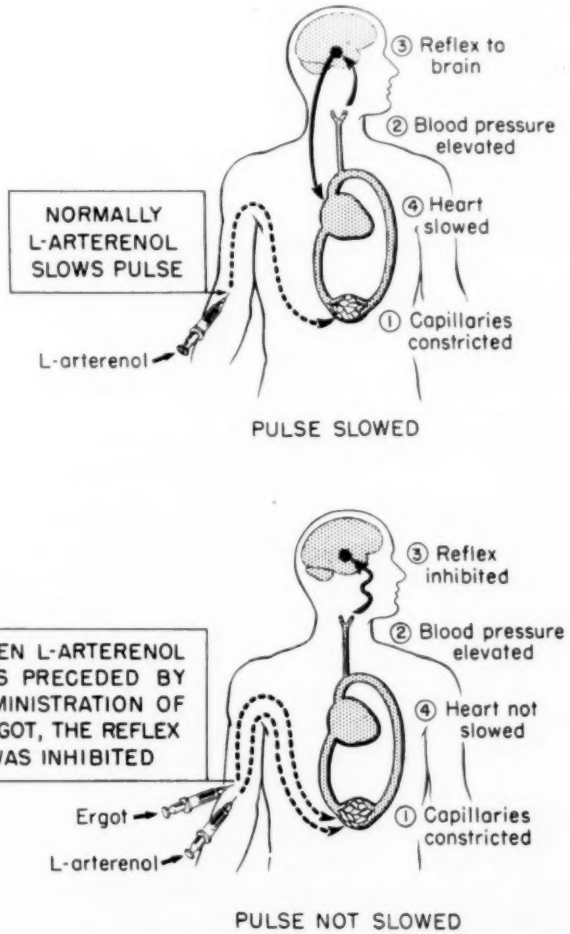

Fig. 3.—The probable mechanism which prevents cardiac deceleration after the hydrogenated ergot alkaloids.

BRAIN DISEASE (CEREBRAL ATROPHY). The findings in this patient were the same as those in the subjects who had received the hydrogenated ergot alkaloids.

THORACOLUMBAR SYMPATHECTOMY (D7 to L2). The vascular reflexes to pain were present in the fingers but were absent in the toes as the sympathectomy included the lumbar but not the highest thoracic ganglia. The systolic and diastolic pressures fell on standing. The mean blood pressure fell likewise. There was marked cardiac acceleration on standing. The venous pressure fell in the arms and the diastolic heart size decreased on standing for 3 minutes. With the patient supine nitroglycerin accelerated the heart and levarterenol slowed it.

VARICOSITIES AND MYASTHENIA GRAVIS. One patient had marked varicosities with pooling of blood in the legs and the other had decreased muscular tone due to myasthenia gravis. Both patients had similar reactions. Supine the vascular reflexes to pain were present in the fingers and toes and the blood volume was normal. The systolic, diastolic, and mean blood pressure fell on standing and cardiac acceleration occurred. Venous pressure fell on standing. Diastolic heart size decreased on standing. With the patients again supine nitroglycerin accelerated the heart and levarterenol slowed it.

BLEEDING PEPTIC ULCER. The digital reflexes were present. The blood volume was decreased. The systolic, diastolic and mean blood pressures fell on standing. The cardiac rate increased markedly. Venous pressure and diastolic heart size decreased on standing. With the patient supine nitroglycerin accelerated and levarterenol slowed the heart rate.

Discussion. Studies of the blood pressure, pulse rate, digital vascular reactions to pain and blood volume showed patterns which were characteristic of patients with orthostatic hypotension due to various causes. In addition studies of venous pressure, diastolic heart size, reactions to nitroglycerin and levarterenol proved of value in clarifying the mechanism of the postural hypotension in certain subjects. In all patients with orthostatic hypotension the systolic, diastolic and mean blood pressure fell on standing. The systolic fall was great with respect to the diastolic fall in patients with the hydrogenated ergot alkaloids and in those with classic orthostatic hypotension due to cerebral disease. The cardiac rate increased in normal subjects but it increased more in the patient after sympathectomy, with pooling of blood in the extremities due to varicose veins, with myasthenia gravis, and with decreased blood volume. There was no significant increase in cardiac rate after the hydrogenated ergot alkaloids or in the patient with brain disease. This is thought to be due to the effect of the drug on the brain and to disease of the cardiovascular center in the brain. In normal subjects a fall in orthostatic pressure in the carotid sinus, aorta or certain vascular structures in the mesentery causes afferent impulses to the brain which stimulate the cardiovascular center to produce vasoconstriction. In patients with brain disease or in subjects receiving the hydrogenated ergot alkaloids this reflex arc was interrupted and the digital vasoconstrictive reflexes to pain were absent. These reflexes were present in the patients with varicose veins, myasthenia gravis and bleeding peptic ulcer. These reflexes may or may not be present in patients with a sympathectomy as the extent of the sympathectomy determines their presence or absence. Blood volume measurements assist in differentiating orthostatic hypotension due

to bleeding from that due to pooling of blood in the extremities. The venous pressure is low or falls on prolonged standing with hypotension due to any cause which results in poor cardiac filling, a decrease in diastolic heart size, a low cardiac output and a further decrease in the arterial blood pressure. Normally nitroglycerin causes a fall in pressure as a result of the direct vasodilating action of the agent on the vessel itself. The hypotension produced in this way results normally in afferent impulses to the brain where the cardiac accelerating mechanism is stimulated and the cardiac rate is increased. This occurred in all patients except those with disease of the brain or those who had received the hydrogenated ergot alkaloids. Levarterenol produced cardiac slowing in all patients except those after the hydrogenated ergot alkaloids and with brain disease. Normally levarterenol produces capillary constriction which raises blood pressure in the carotid sinus and other areas. This produces stimulation of the cardiac inhibiting center of the brain which slows the heart rate. After the hydrogenated ergot alkaloids or in the patient with brain disease, cardiac slowing failed to occur because of the central inhibition of the cardiac inhibiting center. Although the hydrogenated ergot alkaloids have a central depressive action on the sympathetic nervous system other actions of the agent have been described. Typical and atypical headaches associated with arteriosclerotic or essential hypertension were partially or completely relieved with the sublingual administration of the hydrogenated ergot alkaloids in a large percentage of patients (Winsor[11]). Disturbances of cerebral circulation were favorably treated with the hydrogenated ergot alkaloids reported by Popkin[5], Labecki and Busby[3], Strauss[6], Tandowsky[8], and Hollister[2]. Orma[4] reported favorable results with the hydrogenated ergot alkaloids on postural dizziness, employing 3 to 6 tablets daily. Hafkenschiel, *et al.*[1], Taeschler, Cerletti and Rothlin[7] and Weigelin, Niesel and Ossendorf[9] also stated that the hydrogenated alkaloids of ergot improved cerebral circulation.

Summary. Measurements of blood pressure, cardiac rate, digital vasoconstrictor reactions and blood volume showed typical reaction patterns in patients with different types of orthostatic hypotension. The hypotension produced with the hydrogenated ergot alkaloids resembled that due to brain damage. Studies of the reaction patterns made it possible to differentiate postural hypotension due to various causes.

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SOME OBSERVATIONS ON HYPERGLOBULINEMIC PURPURA (WALDENSTROM'S SYNDROME)*

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Hyperglobulinemic purpura is a clinical entity which is characterized by episodic purpura, an accelerated erythrocyte sedimentation rate and an increase in serum gamma globulin.

This disease was first reported by Waldenström[20] in 1943. Subsequent sporadic case reports of this entity have appeared in the European literature (Bender[1], Curtz[3], Dorken[4], Gautier and Maurice[5], Humerfelt[7], Linke[10], Oberste-Lehn[12], Quattrin, Dini and Piccoli[13], Siems and Rausch-Stroomann[15], Waldenström[18], and Weise[22]). A recent authoritative report by Berthoud[2] documented 8 additional European cases. Only one case has been described in the British literature (Kay and Robertson[8]) and only one case describing this syndrome could be found in the American literature (Taylor and Battle[16]). It would seem that with such a paucity of observations on this syndrome in the American literature, additional detailed studies of this disease might be of some interest.

Three patients demonstrating the classical features of hyperglobulinemic purpura have been followed for from one to 5 years in the hematology laboratory of the Department of Medicine of Indiana University Medical Center. These patients were carefully studied for macroglobulins and cryoglobulins. All 3 patients proved to be free of those globulins which yield a clinical picture similar to that seen in the true Waldenström syndrome.

Methods. The following laboratory methods were employed in this study: platelet enumeration (brilliant cresol blue method of Dameshek), bleeding time (Duke), clotting time (Lee and White), erythrocyte sedimentation rate (Wiseman), fibrinogen level (Parafentjev), formol-gel (Bing), one stage prothrombin time and prothrombin consumption time (methods of Quick), protamine-heparin tolerance test (Alexander), and serologic tests for syphilis (Kline, Kahn, Wassermann and Mazzini).

Free electrophoretic analyses were performed on the sera of Cases 1 and 3: veronal-citrate buffer, pH 8.6, ionic concentration 0.1, amperes 0.012, for 180 minutes and 130 minutes respectively. Paper electrophoresis was utilized in Case 2: veronal-citrate buffer, pH 8.6, ionic concentration 0.1, 150 volts for 6 hours.

Ultracentrifugal analyses of the sera were performed with a Spinco model E ultracen-

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trifuge following dialysis for 4 hours and dilution 1:5 with 0.5 M sodium chloride. The centrifuge speed was 60,000 revolutions per minute. Exposures were taken upon reaching top speed and every 16 minutes thereafter.

The "euglobulin test" as described by Waldenström[17] was performed by adding 2 drops of serum to 1 ml. of distilled water. The formation of a cloudy precipitate indicates the presence of an abnormal serum protein, but is of no value in distinguishing one type of dysglobulinemia from another.

Case Reports. CASE 1. This 60-year-old white woman was first admitted to the Indiana University Medical Center in March, 1951, because of aching joints and recurrent purpura on the lower extremities since 1948. The purpura occurred in episodes every 3 to 4 weeks and was increased by exercise. She was also bothered by a constant feeling of dryness in her eyes and mouth. There was no family history of bleeding tendencies.

Physical examination revealed the following abnormalities: There was a brown, patchy pigmentation of the legs and feet with superimposed new petechiae. Multiple small areas of vitiligo were seen over the body and there was a slight fusiform deformity of the fingers.

Laboratory examinations at that time revealed a mild normocytic, normochromic anemia, marked auto-agglutination of the erythrocytes and a moderate increase in the serum globulin. Roentgen examination of the hands showed changes compatible with minimal rheumatoid arthritis.

Since her first visit, she has continued to be bothered by recurrent purpura and painful hand and knee joints. She has, however, been able to perform her duties as a housewife, except for those times when she was hospitalized for observation.

In May, 1956, she was seen for re-evaluation of her illness. Physical examination was essentially the same as before with the exception of an increase in the pigmentation of the lower extremities. The Rumpel-Leede test for capillary fragility was strongly positive.

Laboratory Procedures. The urinalysis was normal and contained no Bence-Jones protein. The hemoglobin was 10.7 gm. %; the erythrocyte count, 4.0 million per c.mm.; and the reticulocyte count, 1.4%. The total leukocyte count was 4,900 per c.mm. with 88% neutrophils, 2% eosinophils, 4% lymphocytes, and 6% monocytes. The platelet count was 332,000 per c.mm. and the erythrocyte sedimentation was 0.0 mm. per minute. Marked auto-agglutination of the erythrocytes was present.

Examination of the sternal bone marrow revealed normal cellularity with a slight increase in lymphocytes. There was no increase in, nor morphologic alteration of the plasma cells.

The bleeding time was 1 minute and 10 seconds; the clotting time, 12 minutes and 30 seconds. Clot retraction was firm in one hour and there was no lysis of the clot after incubation at 37° C. for 24 hours. The fibrinogen level, prothrombin time, prothrombin consumption time, and protamine-heparin tolerance test were normal.

Cold agglutinins could not be demonstrated and serologic tests for syphilis were negative. The total blood nonprotein nitrogen, serum alkaline phosphatase, and bromsulphalein dye excretion were normal.

The formol-gel reaction was present in 30 minutes and the euglobulin test was positive. No cryoglobulin was present. The thymol turbidity, cephalin flocculation, and serum bilirubin determinations were considered unsatisfactory because of the precipitate formed upon water dilution of the serum. The total serum protein was 8.60 gm. %; the albumin 4.15 gm. %; the globulin 4.45 gm. %. Free boundary electrophoresis (Fig. 1) of the serum revealed an abnormally high rounded gamma globulin peak which measured 35% of the total protein by planimetry.

CASE 2. This 63-year-old white woman was first seen in our laboratories November 11, 1955, because of persisting purpura of the lower extremities and enlargement of the spleen, both symptoms of 2 to 3 years' duration. She had been seen by a number of physicians who had postulated that she was suffering from chronic lymphocytic leukemia. In treating this disease, she had had splenic irradiation therapy in April, 1955. The exact response to her irradiation therapy could not be determined but she stated she felt subjectively unimproved.

During the course of her illness, she stated she had been troubled by recurrent bouts of purpura which appeared predominantly on the lower extremities and below such areas of compression as might be encountered with garters or girdles. She stated that she had a "nervous, all gone feeling" with considerable tension and anxiety preceding each of her episodes of purpura. She stated that her legs would become pruritic and somewhat painful and then would break out with small petechial hemorrhagic spots which had, over the period of years, gotten progressively

more marked, and had left residual, brownish pigmented areas distributed generally over both of her lower extremities.

She stated that she had been taking some type of pain pills which she thought were aspirin tablets and in addition, she had been receiving "shots" for menopausal symptoms.

In reviewing her history by symptoms, she revealed that she had, for at least 10 to 15 years, been troubled with arthritis which was deforming and was associated with intermittent reddening and swelling of the joints. These arthritic complaints were confined chiefly to her hands and feet but she had palpable 6 cm. below the left costal margin. The liver was palpable 3 cm. below the right costal margin. A Rumpel-Leede test was strongly positive. The initial blood count revealed the following values: Red blood cell count, 2.5 million per c.mm.; white blood count, 4,010 per c.mm.; hemoglobin, 11.7 gm. %; platelets, 500,000 per c.mm.; and reticulocytes, 8.5%. The peripheral differential showed a slight increase in mature lymphocytes but otherwise was not remarkable. A bone marrow aspirate was obtained with considerable difficulty and only a scattered number of small fragments was

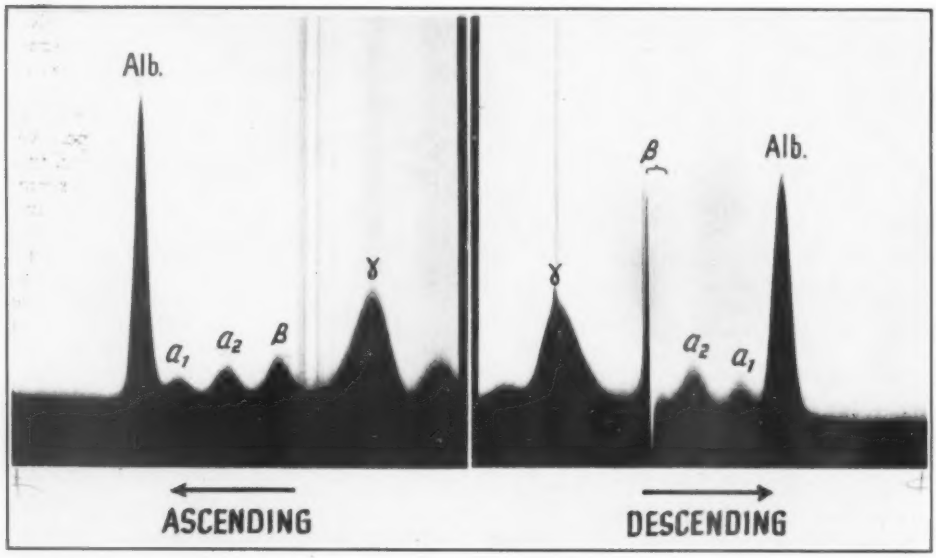

Fig. 1.—Free boundary electrophoresis of the serum in Case 1. Note the large rounded gamma zone (35% of the total protein).

occasionally noted them in her knees and shoulders. She stated that she had not been treated with anything other than pain pills for her arthritis.

There was a history that she had sustained a traumatic fracture of her back and, as a result of this, she found it necessary to wear a back brace. Initially, on physical examination, she showed a rather diffuse brown pigmentation of the skin which was most marked on the lower extremities. Her legs, from the knees to shoe tops, demonstrated innumerable petechiae. Enlargement of cervical and axillary lymph nodes was detected. The nodes varied in size from 1 to 2 cm. and were nontender and discrete. The spleen was found. There was some slight increase noted in lymphocytes on this initial examination of the bone marrow and there were a few abnormal reticulum cells which were not typical of the type seen in reticulum cell sarcoma. There was considerable rouleaux formation of red cells.

An initial roentgenologic study of the chest revealed uncoiling of the aorta with uniform de-mineralization of thoracic bones. Roentgenray examination of the dorsal spine showed a healed compression fracture of the tenth thoracic vertebral body. Additional studies revealed the following laboratory values: Erythrocyte sedimentation rate by the Wiseman technique revealed a value of 0.8

(normal 0.2–0.4). Bleeding time was 2 minutes, 55 seconds; Lee and White coagulation time, 11 minutes; clot retraction, firm at 2 hours. No lysis of the clot was found after incubation at 37° C. for 24 hours. Fibrinogen level, 0.340 gm. %; prothrombin time, 100%; cold agglutinins, negative; serological test for syphilis, negative; nonprotein nitrogen, 49 mg. per 100 ml.; alkaline phosphatase 3.5, King and Armstrong units; cryoglobulin, none; euglobulin and formol-gel, negative; thymol turbidity, 3 units; cephalin flocculation, negative; bilirubin, direct 0.2 mg. per 100 ml., indirect 0.3 mg. per 100 ml., total 0.5 mg. per 100 ml.; serum protein, albumin 4.41 gm. %; globulin, 1.99 gm. %, total 6.40 gm. %. Paper electrophoresis (Fig. 2) revealed a gamma total of 27% of the total protein. Ultracentrifugal analysis (Fig. 4) revealed an S–7 of 24%. She was started on steroid therapy, receiving 5 mg. of Prednisone every 8 hours. On this program, there was a re-establishment of a normal erythropoiesis with improvement of the erythrocyte count to 4.6 million per c.mm. with 14.5 gm. % of hemoglobin. This also was associated with a decrease in her arthritic attacks and improved strength and feeling of well-being.

There has been noted no decrease in the number of petechiae although she has had considerable improvement in the pain in her lower extremities by the wearing of elastic stockings. These elastic stockings seem to have slightly minimized the number and severity of her petechial episodes. She has maintained normal weight and reasonable appetite on this course of therapy.

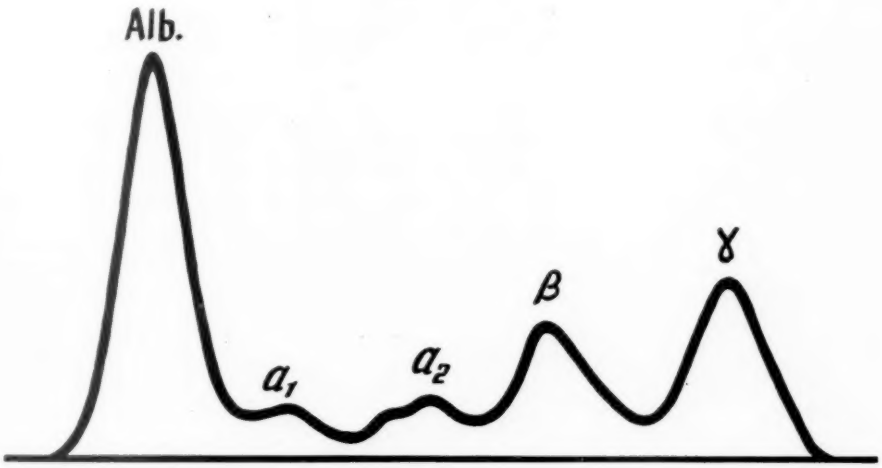

Fig. 2.—Densimetric drawing of the paper electrophoretic pattern of the serum in Case 2 The gamma zone represents 27% of the total protein.

CASE 3. This 39-year-old white woman was first admitted to the Indiana University Medical Center on March 20, 1956, because of a hemorrhagic rash, enlarged cervical lymph nodes, and anemia.

In December, 1950, an abdominal mass had been discovered during a routine physical examination. Exploratory laparotomy at another hospital revealed a gastric tumor which was simply excised. This was said to be a malignant growth. She was without symptoms until July, 1953, when she noted the onset of purpuric syndrome, consisting of a recurrent, petechial rash of the lower extremities. With each episode the extremities became painful and mildly swollen. Each episode was preceded by a feeling of malaise and fatigue. These petechiae were increased during periods of physical exertion. At the onset of her purpuric syndrome, she was found to have a recurrence of her gastric tumor. This was excised and described as consisting of necrotic inflammatory tissue. One year prior to her last admission, the petechiae spread to involve other areas of her body. She became increasingly more tired and cervical lymphadenopathy appeared. A biopsy of one of these nodes was said to reveal "lymphoma." She received Roentgen-ray

therapy to her neck at this time as well as a transfusion of 4 units of blood. Corticosteroid therapy was started. A slight regression in the cervical adenopathy occurred; however, the episodic purpura spread to involve the skin of her upper extremities, trunk, face and conjunctivae. She had had night sweats for the past year and the sensation of dryness of the eyes and mouth. There was no family history of bleeding tendencies.

Physical examination revealed the following pertinent data: Her general appearance suggested early Cushing's syndrome. There were fresh bilateral conjunctival hemorrhages. The skin of the legs and feet exhibited marked patchy, brownish pigmentation. Many petechiae, singly and coalescing, were seen over the body. These were most numerous on the extremities. There was generalized peripheral lymphadenopathy most prominent in the left cervical chain. The nodes were nontender, nonfixed, firm, and varied in size from 0.25 to 3 cm. in maximum diameter. The liver edge was firm and rounded and could be palpated at the right costal margin on deep inspiration. The Rumpel-Leede phenomenon was present.

Laboratory Procedures. The urine contained a trace of albumin, but no Bence-Jones protein. The hemoglobin was 8.6 gm. %; the erythrocyte count 2.53 million c.mm.; and the reticulocyte count, 10.7%. The total leukocyte count was 2 800 per c.mm. with 56% neutrophils, 36% lymphocytes, and 6% monocytes. The platelet count was 457,950 per c.mm. and the erythrocyte sedimentation rate was 0.7 mm. per minute. Marked autoagglutination of the erythrocytes was present.

The bleeding time was 55 seconds, the clotting time 5 minutes and 40 seconds. Clot retraction was firm in 2 hours; however, upon incubating the clot at 37° C. for 24 hours, a slight amount of lysis occurred. The fibrinogen level, prothrombin time, prothrombin consumption time, and protamine-heparin tolerance test was normal.

Cold agglutinins could not be demonstrated and serologic tests for syphilis were negative. The total blood nonprotein nitrogen, serum alkaline phosphatase, and serum bilirubin were normal. The bromsulphalein dye retention in 45 minutes was 24%.

The euglobulin test was positive; the formol-gel reaction and cryoglobulin could not be demonstrated. The thymol turbidity and cephalin flocculation determinations were unsatisfactory because of clouding of the serum when diluted with water.

The total serum protein was 7.15 gm. %; the albumin 3.58 gm. %; the globulin 3.57 gm. %. Free boundary electrophoresis (Fig. 3) of the serum demonstrated an increase in the gamma globulin fraction comprising 31% of the total protein.

Ultracentrifugal analysis (Fig. 4) of the serum demonstrated an increased amount of protein component sedimenting at a Svedberg constant of 7 (31% of total protein).

Roentgen examination of the stomach demonstrated moderate fixation of the lesser curvature and a 2 cm. filling defect in the antrum, suggesting the presence of a polyp. A slight rotation of the right kidney was seen on the excretory pyelogram.

The initial sternal bone marrow examination revealed hypercellularity of all normal elements. A repeat examination 30 days after admission demonstrated extensive infiltration of the marrow by sarcomatous appearing reticulum cells (Fig. 5*B*).

Course in Hospital. In view of the evidence of increased destruction of the cellular elements of her blood and hyperplasia of the bone marrow, a splenectomy and abdominal exploration were performed. At the time of surgery, it was noted that the omentum, mesentery, and retroperitoneal tissues were infiltrated with large masses of tumor. A biopsy of one of these masses revealed the histologic picture of reticulum cell sarcoma (Fig. 5*A*). The spleen weighed 271 gm. and microscopically demonstrated only perifollicular congestion.

Although her peripheral blood values became normal after splenectomy, she began to lose weight and developed a persistent right pleural effusion. Forty-five days following her admission, she expired because of an exsanguinating gastrointestinal hemorrhage.

The pertinent findings at necropsy included the infiltration of the above mentioned abdominal structures with reticulum-cell sarcoma. Sarcomatous infiltration of the stomach was present as well as superficial ulcerations of the gastric mucosa. An open artery was seen at the base of one of the ulcerations. The liver weighed 2500 gm. and demonstrated sarcomatous infiltration in the periportal areas.

Discussion. Hyperglobulinemic purpura probably occurs more frequently than the sparse reports in the literature would imply. The syndrome has been observed most often in middle-aged women; however, men are not excluded. The prominent and consistent

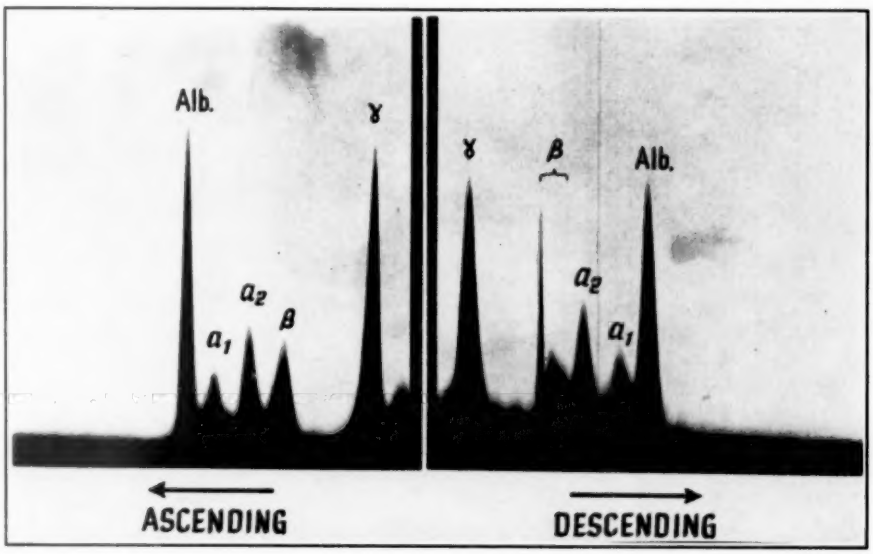

Fig. 3.—Free boundary electrophoresis of the serum in Case 3. The gamma zone (31% of the total) comprises an area greater than the albumin.

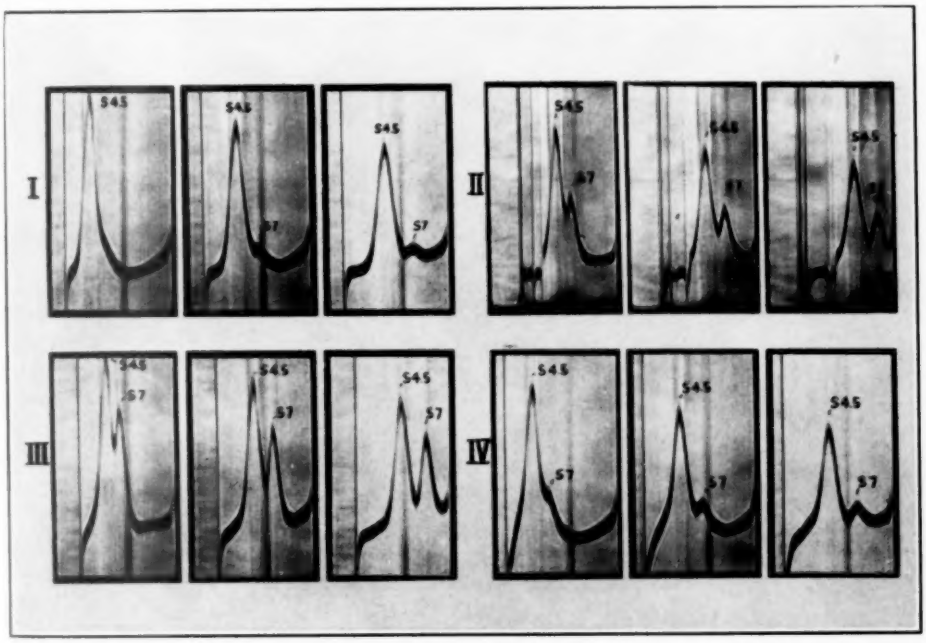

Fig. 4.—Ultracentrifugal patterns of 4 serums. I. Serum of a normal individual, S–7 comprising 31% of the total curve. II. Serum of Case 3, S–7 comprising 31% of the total curve. III. Serum of Case 1, S–7 comprising 42% of the total curve. IV. Serum of Case 2. S–7 comprising 24% of the total curve.

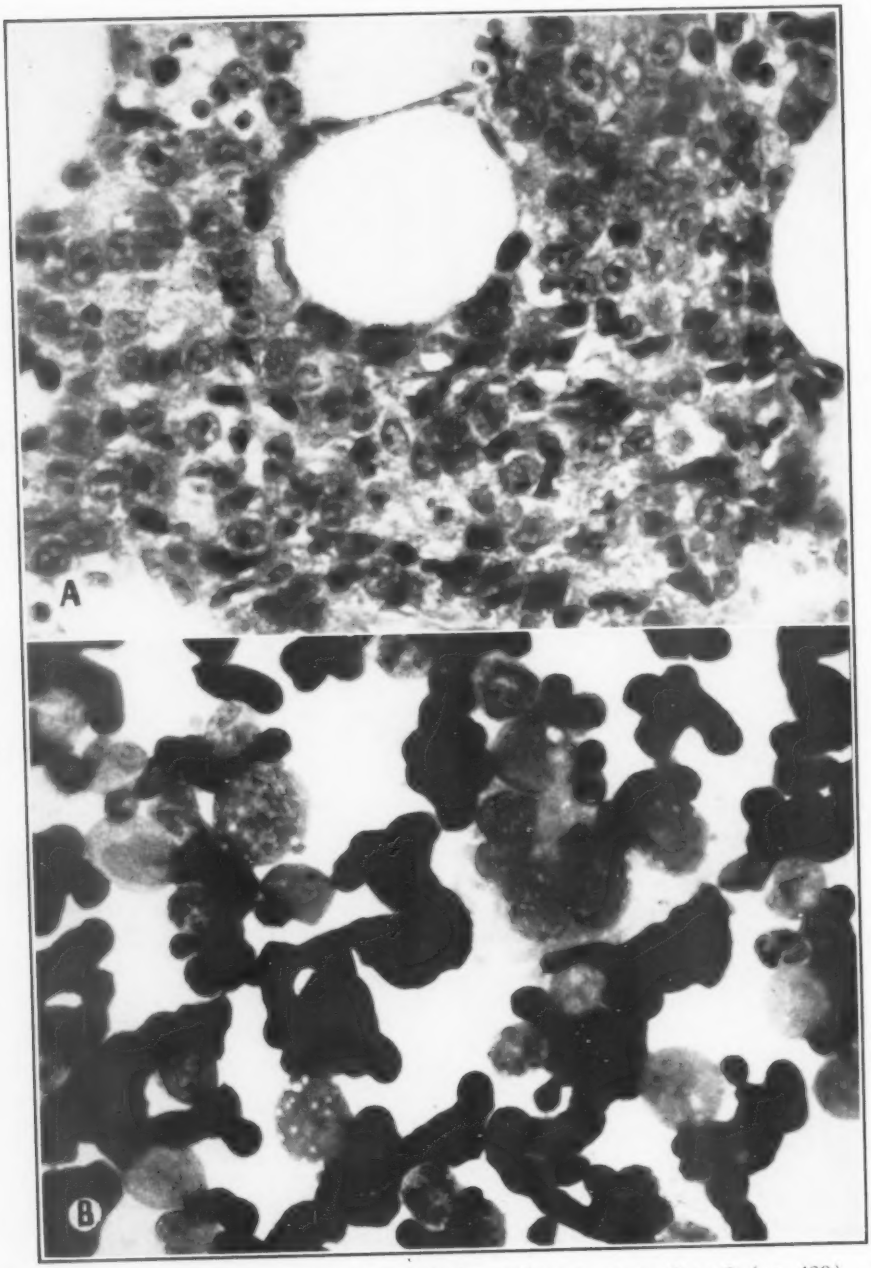

Fig. 5.—(*A*) Mesenteric mass showing reticulum-cell sarcoma in Case 3 (× 430). (*B*) Bone marrow preparation illustrating invading reticulum-cell sarcoma in Case 3 (× 970).

finding is that of episodic showers of petechiae. The petechiae may occur on all parts of the body, but are most numerous on the lower extremities. Frequently, the intracutaneous hemorrhage is heralded by a prodrome of malaise. Most often there is no precipitating factor for each episode; however, an increase in physical exertion, the wearing of constrictive clothing, and prolonged periods of standing may precede or exaggerate the purpura.

The bleeding tendency is limited to the skin in most instances. This is apparently due to an abnormality of the capillary wall as evidenced by the presence of the Rumpel-Leede phenomenon in all cases and the absence of a clear-cut coagulation mechanism defect. One of our patients (Case 3) exhibited periodic swelling of various parts of her body. It was suspected that this might be due to intramuscular bleeding. Serious systemic bleeding has not been reported.

The sensation of dryness of the eyes and mouth are common complaints. Sjögren (Siems and Rausch-Stroomann[15]) and Mikulicz (Curtz[3]) syndromes have been reported, in conjunction with the Waldenström syndrome. Possibly the abnormal protein interferes with the secretory function of the salivary and lacrimal glands.

Generalized lymphadenopathy is a common finding. Only nonspecific reticulum hyperplasia has been reported (Horster[6] and Waldenström[18]). Moderate enlargement of the spleen and liver may occur. Waldenström[18] observed a 23-year-old white woman with hyperglobulinemic purpura who demonstrated acquired hemolytic anemia. Pathologic examination of her spleen revealed an increase in reticular elements.

The syndrome tends to run a chronic and benign course. Waldenström[18] has followed several patients 10 to 20 years with no evidence of associated disease. However, Gautier and Maurice[5] have observed the syndrome associated with sarcoidosis in one patient. In Case 3 in this presentation we found hyperglobulinemic purpura occurring in a patient with disseminated reticulum cell sarcoma.

Examination of the peripheral blood usually reveals a normocytic, normochromic anemia of moderate degree. Slight to moderate auto-agglutination of the erythrocytes is frequently present. An accelerated erythrocyte sedimentation rate is a constant feature. The total leukocyte count usually shows no deviation from normal. Procedures concerning the clotting mechanism such as the platelet count, clotting time, clot retraction, prothrombin time, prothrombin consumption time, and the fibrinogen content of the blood are within normal limits. The bleeding time is not prolonged and circulating anticoagulants have not been demonstrated.

Nonspecific tests of abnormal protein such as Bence-Jones proteinuria, the formol-gel reaction, and the euglobulin test are of interest, but of little aid in diagnosis since they are commonly present in many chronic diseases involving the reticuloendothelial system. Liver function tests are usually within normal limits, except for the flocculation tests which may be abnormal because of cloudiness which appears when the serum is diluted with water.

The total serum protein may be within normal limits or moderately elevated. The serum albumin is usually slightly decreased, and the serum globulin both relatively and absolutely increased.

Electrophoretic analysis of the serum places the increased globulin protein in the gamma fraction. Most

often the gamma peak is "rounded" suggesting an heterogenous composition. This is in contradistinction to the "sharp" peak associated with multiple myeloma and macroglobulinemia. Waldenström[20] observed that this "rounded" peak is also seen in chronic virus infections and suggested that hyperglobulinemic purpura may be the manifestation of such an infection.

In normal individuals, the gamma globulin comprises 15% or less of the total protein. In our patients, the gamma fraction was in excess of 26%. In hyperglobulinemic purpura, the gamma globulin has been reported to comprise as much as 75% of the total protein[5].

Ultracentrifugal analysis has been infrequently reported. The characteristic pattern reveals an abnormally high protein component sedimenting with a Svedberg constant of 7 (Waldenström *et al.*[21]).

Bone marrow examination is necessary to exclude multiple myeloma. Marrow hypoplasia (Taylor and Battle[16]), lymphocytic infiltration (Waldenström[18]) of the marrow and increased numbers of reticulum cells containing inclusion bodies (Horster[6]) in the marrow have been reported. Frequently, no abnormalities are seen.

It is essential to the diagnosis of hyperglobulinemic purpura that cryoglobulinemia and macroglobulinemia be excluded since bleeding tendencies are also common with these protein abnormalities. The intracutaneous hemorrhage of cryoglobulinemia is usually precipitated by exposure to cold and often associated with Raynaud's phenomenon. When the serum from these patients is cooled, a white precipitate forms. The serum must be incubated at 3° C. for 3 days with no evidence of precipitate to exclude entirely cryoglobulinemia.

Macroglobulinemia is most often encountered in old men and is characterized predominantly by hemorrhage from the mucous membranes of the nasal mucosa, pharynx, and gastrointestinal tract, although cutaneous hemorrhage may occur. The demonstration by ultracentrifugation of a protein component of 15–S or greater comprising over 5% of the total protein is necessary for the diagnosis (Mackay *et al.*[11]).

Hyperglobulinemic purpura represents a peculiar response (possibly allergic because of its episodic character) of an irritated reticuloendothelial system which may or may not accompany a definite disease process. The association of an increase in the gamma globulin with capillary fragility has yet to be explained. Waldenström[18] suggests that the abnormal production of gamma globulin occurs at the expense of a globulin necessary for the integrity of the capillary wall. Schmengler and Esser[14] hypothecate that the capillary damage is a direct result of the abnormal globulin upon the endothelial wall.

Summary. Three patients demonstrating the syndrome of hyperglobulinemic purpura have been presented. The striking clinical feature is that of episodes of purpura (chiefly on the dependent parts) occurring over a number of years. Two of the patients (Cases 1 and 2) exhibited the benign and chronic course characteristic of the syndrome. Case 3 is unique in being the first reported case of this disorder associated with, and possibly due to, a disseminated reticulum-cell sarcoma.

The only defect in the hemostatic mechanism which could be detected was that of capillary fragility. The erythrocyte sedimentation rate was uniformly accelerated. An abnormality of the serum protein was manifested electrophoretically by an increase in the gamma fraction and ultracentri-

fugally by an increase in the 7–S component. No cryoglobulins or macroglobulins were detected.

It is suggested that this serum protein abnormality is related to the loss of integrity of the capillary wall.

ACKNOWLEDGMENTS: We are deeply indebted to Dr. Harold Taylor and the Pitman-Moore Research Laboratories for the free boundary electrophoretic patterns, and to Dr. E. O. Davisson, Research Laboratories, Eli Lilly and Company for the ultracentrifugal analyses.

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SUMMARIO IN INTERLINGUA

Observationes in Re Purpura Hyperglobulinemic (Syndrome de Waldenstrom)

Es presentate le casos de tres patientes demonstrante le syndrome de purpura hyperglobulinemic. Le plus frappante characteristica clinic es episodios de purpura (principalmente in le partes dependente) que occurre in le curso de plure annos. Duo del patientes exhibiva le benigne curso chronic que es characteristic del syndrome. Le tertie caso es unic in tanto que illo es le prime unquam reportate in que le disordine es associate con (e possibilemente causate per) un disseminate sarcoma de cellulas reticular.

Le sol detigibile defecto del mechanismo hemostatic esseva un defecto del fragilitate capillar. Le sedimentation erythrocytic esseva uniformemente accelerate. Un anormalitate del proteina del sero esseva manifeste electrophoreticamente in un augmento del fraction gamma e ultracentrifugemente in un augmento del componente 7–S. Nulle cryo- o macroglobulinas esseva detegite.

Es signalate le possibilitate que iste anormalitate del sero es relationate al perdita de integritate del pariete capillar.

EXTREMELY RAPID ARRHYTHMIAS AND REGULAR TACHYCARDIAS IN PAROXYSMS IN PATIENTS WITH AND WITHOUT ACCELERATED A–V CONDUCTION

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The most common type of "heart attack" complained of by otherwise apparently normal individuals consists of very rapid, regular or irregular heart action. In addition to palpitation, if the rate is extremely high, the patient may experience giddiness, weakness, vertigo, visual disturbances and even syncope. Extremely rapid rates are the rule and clinically strongly suggest the presence of accelerated A–V conduction.

The attacks are often of short duration and so transient that symptoms are only momentary and it is difficult to establish the type of mechanism responsible. If it is of sudden onset and regular at rates about 160 or more per minute and stops suddenly within a beat we infer a paroxysm of atrial tachycardia or flutter; if irregular we suspect a paroxysm of atrial fibrillation. If the ventricular rates are in the neighborhood of 200 we suspect accelerated A–V conduction.

We always exert every effort to get an electrocardiogram during the attack and the analysis of this is usually comparatively simple. Occasionally the interpretation of the electrocardiogram is much more difficult and errors in diagnosis, prognosis, and emergency therapy result. In rare instances the recordings of regular or irregular, bizarre, broad complexes at a rapid rate are most alarming to the bedside electrocardiographer. This is particularly common in patients with the seemingly accelerated A–V conduction disturbance. Examples of such disorders that have excited us will be described in this report.

Case Reports. CASE 1. T.M.R.'s first case, seen in association with R. P. Martin, M.D. and Mel H. Levin, M.D., was a white man, aged 22 years, a Pfc (J.E.R.) in the USMC, who had an episode of rapid irregular palpitation while playing baseball. He felt slight substernal discomfort but little faintness and mild coolness of his hands. In previous attacks since the age of 8 years, the rapid heart action, he felt, had always been regular.

He walked into the hospital and to the heart station. As soon as the electrocardiogram showed broad irregular variable QRS complexes at a rate of 240 to 280 per minute was traced he was put to bed. His peripheral pulses were barely palpable, small and irregular at a rate of about 70 per minute, while on auscultation irregular heart sounds were audible at about twice the pulse rate. The blood pressure was maintained at 110 mm. Hg systolic and 70 mm. Hg diastolic. A diagnosis of chaotic heart action, atrial fibrillation and bundle branch block was made. The maintained normal blood pressure and absence of signs of collapse clinically ruled

out ventricular fibrillation which diagnosis the electrocardiographer had made on the appearance of the bizarre electrocardiograms.

Therapy in the emergency consisted of procaine amide, 1 gm. intramuscularly. Four hours later 1 gm. of procaine amide was given intravenously and the rate slowed to 150 but the electrocardiographic pattern was the same as it had been before medication. See Fig. 1A.

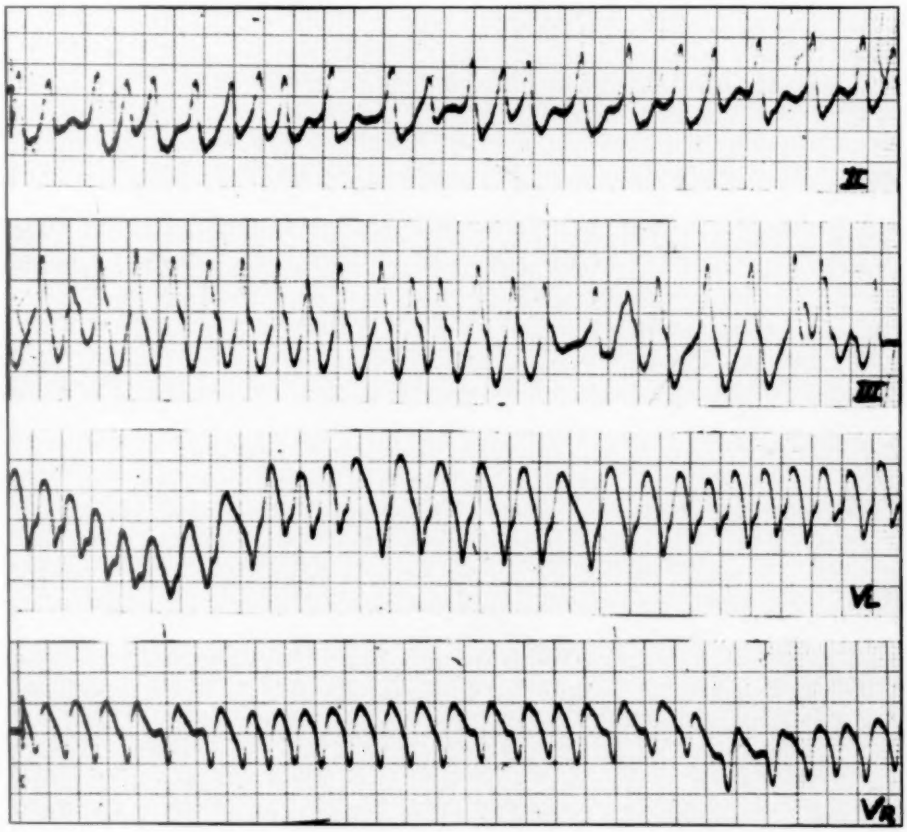

Fig. 1A.—J.E.R., 20 yr. Pfc., USMC. Leads 2, 3, aVL and aVR during paroxysm of pseudoventricular fibrillation.

Seconal 0.1 gm. was given every 4 hours and morphine sulfate, 16 mg. was given subcutaneously.

Fifteen hours after the onset when the rate had risen above 150, another 0.5 gm. of procaine amide was given intravenously. Belching and vomiting occurred all night. At 20 hours after the onset the pulse was noted to be regular and the electrocardiogram, Fig. 1*B*, showed sinus arrhythmia with accelerated A–V conduction of Wilson, Wolff, Parkinson and White.

CASE 2. A white woman, age 33, seen with R. E. Gray, M.D. (Mrs. D.F.V.) mother of 3 children, was having one or two short attacks of rapid irregular heart action daily. She had had episodes all of her life, but the attacks had become more severe. She had her first severe attack of rapid irregular heart action, severe palpitation, shortness of breath and weakness 4 months after her second parturition 12 years previously. She did not collapse but was hospitalized for extreme dyspnea, had to have oxygen and was rapidly digitalized. Carotid sinus massage was ineffective. The attack lasted for 48 hours.

She had had two other severe prolonged attacks which required hospitalization. She was hospitalized from 2 to 8 January 1954 and from 19 to 24 January 1954. She had had attacks of 30 minutes' duration about every 6 months. Shortness of breath and pain in the precordium radiating through to the back had been noted during and after the severe attacks. Her basal metabolic rate had been found high and she had had a course of antithyroid drug. She had drunk two cups of coffee a day and smoked a package of cigarettes a day. She had had pneumonia at the age of 28 years and scarlet fever and "influenza" in early childhood.

Physical examination showed a young woman of large proportions. She measured 69 inches and weighed 161 pounds. The lungs were resonant and clear, the heart was not enlarged; the sounds were loud, even when the heart action was very rapid and grossly irregular and the blood pressure was maintained at 110 mm. Hg systolic and 64 mm. Hg diastolic.

The abdomen was slightly protuberant but the liver and spleen were not palpable and no tenderness was elicited. There was some swelling of the right leg from a posthysterectomy thrombophlebitis 4 years previously.

Electrocardiograms showed pseudoventricular fibrillation with short periods of narrow QRS complexes at rapid rate and with no P but positive F waves. Most of the ventricular complexes were broad, bizarre, varying in form and frequency. Between attacks the electrocardiograms showed short P–R inter-

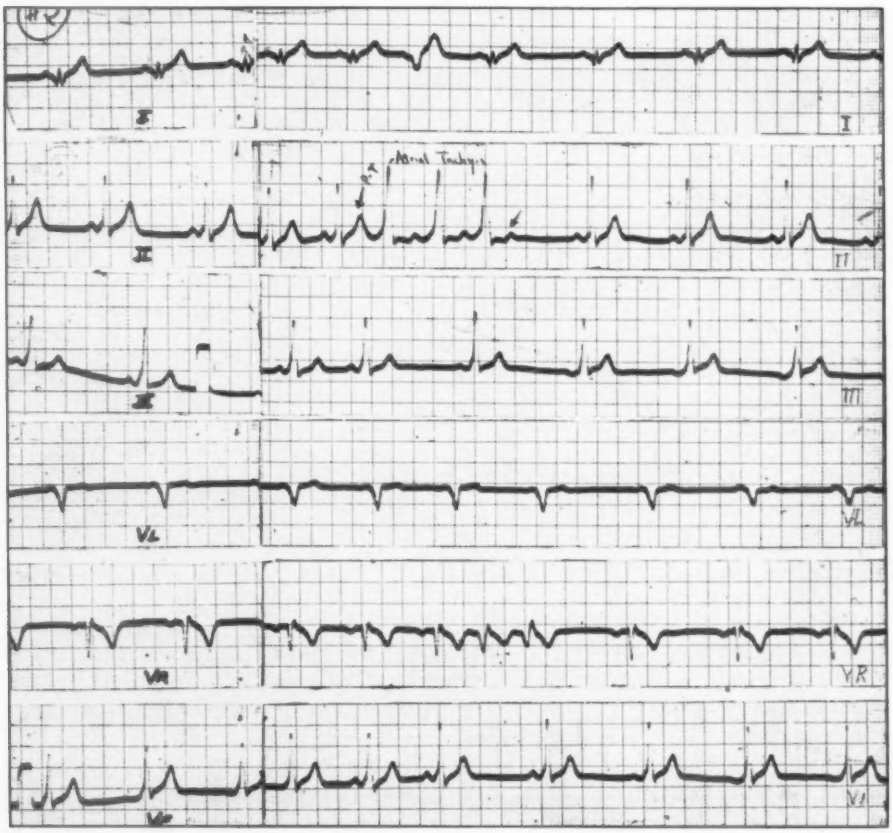

Fig. 1*B*.—J.E.R., 20 yr. Pfc., USMC. All leads after Pronestyl. Note that aberrant QRS complexes of two premature atrial beats are exactly the same as those recorded in 1A, lead 3.

vals, slurred R-waves, broad QRS complexes and left axis deviation.

CASE 3. G.S., a white man, aged 33, seen with William A. Levin, M.D. had been perfectly well until January 10, 1952. He was very apprehensive during the preparation and after venesection for a blood donation. He felt palpitation and lapsed into unconsciousness and had a convulsion.

The attending physician could feel no pulse and get no blood pressure and felt that he could hear no heart sounds. The pulse became palpable but was small, rapid, irregular with a deficit in that irregular rapid heart sounds at almost twice the rate could be heard on auscultation of the precordium. The blood pressure was difficult to obtain.

Consciousness returned promptly, he had no chest pain, no dyspnea, cough or expectoration but palpitation continued. An electrocardiogram taken within 30 minutes was reported to show ventricular fibrillation and this erroneous report caused exaggeration of the situation.

Pronestyl, procaine amide 500 mg. was given intravenously and the patient responded spectacularly as the rapid irregular heart action was promptly abolished.

The electrocardiogram taken during the collapse showed a rate of 250 to 320 per minute, and was interpreted as showing pseudoventricular flutter or fibrillation. Subsequent electrocardiograms showed typical Type I, Wilson, Wolff, Parkinson and White syndrome.

CASE 4. A white man, aged 26 years (A.G.B.) seen with A. R. A. Kerim, M.D., complained of irregular pounding of the heart that came on after returning from a "fishing trip." Besides the irregular palpitation he had felt a heaviness in the chest and giddiness. The pulse was barely palpable and very irregular at a questionable rate of 70 or 80 per minute and on precordial auscultation the heart sounds were so rapid and so irregular that they were not counted. The blood pressure was obtained with difficulty and was low, systolic 100, diastolic 55 mm. Hg. There was no real dyspnea, cough or collapse.

An emergency room electrocardiogram was taken and was thought to show ventricular fibrillation and he was immediately hospitalized.

On admission the patient did not seem to be *in extremis*. There was no evidence of collapse or heart failure, no engorgement of the neck veins, no signs of pulmonary edema. He was of athletic build. His pulse persisted small and irregular and the heart sounds could be counted at over 200 per minute, irregular in rhythm but occasionally regular. He gave a history of having had similar but fleeting attacks of palpitation in the past especially when overworking with loss of sleep for 4 years up to 2 years previously, but none for 2 years preceding this most prolonged attack.

The electrocardiograms showed pseudoventricular fibrillation and tachycardia at a rate of 250 per minute.

Procaine amide 1000 mg. I.V. decreased and eliminated the aberrant ventricular complexes. Atrial fibrillation with supraventricular complexes appeared transiently but cleared and the rhythm became regular at 78 per minute. The electrocardiogram then showed typical Wilson, Wolff, Parkinson and White complexes. Quinidine sulphate 0.2 gm. q.i.d. was given as a prophylactic.

CASE 5. A white girl, aged 12 (I.L.) seen with J. L. Knighton, M.D., had a cold and during a coughing attack she noted the onset of a most severe attack of fluttering in the chest which caused extreme weakness. She was promptly hospitalized as she went into shock and showed pallor and cyanosis. Her pulse rate was reported to be too high to count and her heart action was extremely rapid, but was counted at 240 and regular. Her blood pressure was 88/80. An electrocardiogram was thought to show ventricular flutter or tachycardia at 240 per minute.

She was given quinidine and phenobarbital which caused nausea and vomiting. Digitoxin 1.2 mg. was given intramuscularly and quinidine continued by mouth. Fever and rales in the chest developed and were considered to be evidences of a virus pneumonia. After 27 hours the attack spontaneously stopped. One year later a similar attack lasted 7 hours, responded to procaine amide 250 mg. intramuscularly with sodium phenobarbital. Almost a year later a third attack quite similar with a rate of 250 per minute occurred. Procaine amide 250 mg. stopped the attack within 30 seconds after intravenous injection.

She had had attacks at 11, 12, 13, 14 and 15 years, the severe ones just after she started her menarche. The last attack was stopped by carotid sinus pressure in her 15th year. She was seen at age 18 years and had been free of attacks for 3 years.

Electrocardiograms showed paroxysmal pseudoventricular flutter or tachycardia. Between attacks, the electrocardiograms showed the Wilson, Wolff, Parkinson and White syndrome in a modified form.

CASE 6. A white boy, aged 16 years (R.B.) seen with P. H. McKay, M.D., complained of attacks of rapid palpitation, generalized weakness, nausea and vomiting. These episodes had recurred every 1 or 2 months for 6 years and had lasted from 2 to 20 hours. An electrocardiogram was taken by Dr. Pat McKay of San Antonio and the tentative diagnosis of paroxysmal ventricular tachycardia, at a rate of 230 per minute, was made. The disorder stopped spontaneously before any drug was given.

Physical examination had shown no dyspnea, orthopnea, engorgement of the neck veins, pulmonary edema or any signs of heart failure. There was slight pallor and low blood pressure 100/70, but no evidence of shock. The heart was not enlarged but a systolic thrill and a very loud, slightly rough, grade III, blowing systolic murmur was heard with its maximum intensity in the fourth left ICS at the sternal border transmitted to the tricuspid and to the mitral area. An interventricular septal defect was considered to be the most likely defect.

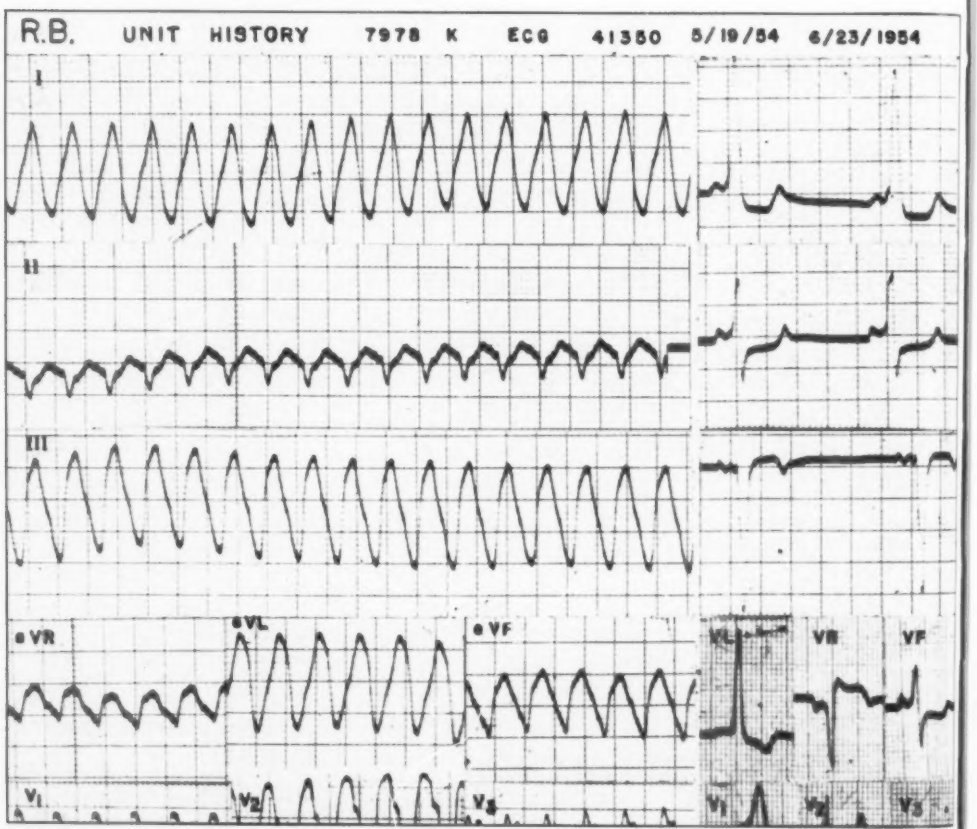

Fig. 2.—R.B., 16 yr. white male showing pseudoventricular tachycardia. Note the absolute regularity. In certain leads notches probably R-waves occur at the same place in each broad QRS complex. At the right of the figure are the standard leads taken during normal sino-atrial rhythm with Wilson, Wolff, Parkinson and White syndrome.

Electrocardiograms (Fig. 2) showed ventricular complexes at the rate of 230 per minute. In some leads definite P-waves could be identified with each complex indicating a supraventricular pseudoventricular tachycardia.

Electrocardiograms between attacks showed typical short P–R, slurred R delta waves, and compensatory broad QRS of Wilson, Wolff, Parkinson and White.

COMMENT. As we record electrocardiographically at the bedside rapidly recurring regularly spaced broad ventricular complexes, we are prone to diagnose ventricular tachycardia which is a serious disorder and warrants emergency measures. When the ventricular complexes are of varying bizarre forms in irregular rapid sequence we fearfully concede that the delirium cordis or chaotic action represents ventricular fibrillation and impending exitus.

Then when we look at the patient and see that he is not cadaveric, in fact, is not even in shock, has some pink color, responds to questions, breathes only slightly rapidly and has a blood pressure that is maintained and an irregular, but slower pulse, we are reassured. We are doubly reassured when we remember the fact that there are pseudoventricular fibrillation and tachycardias which, though serious, are not fatal as a rule and will respond well to therapy.

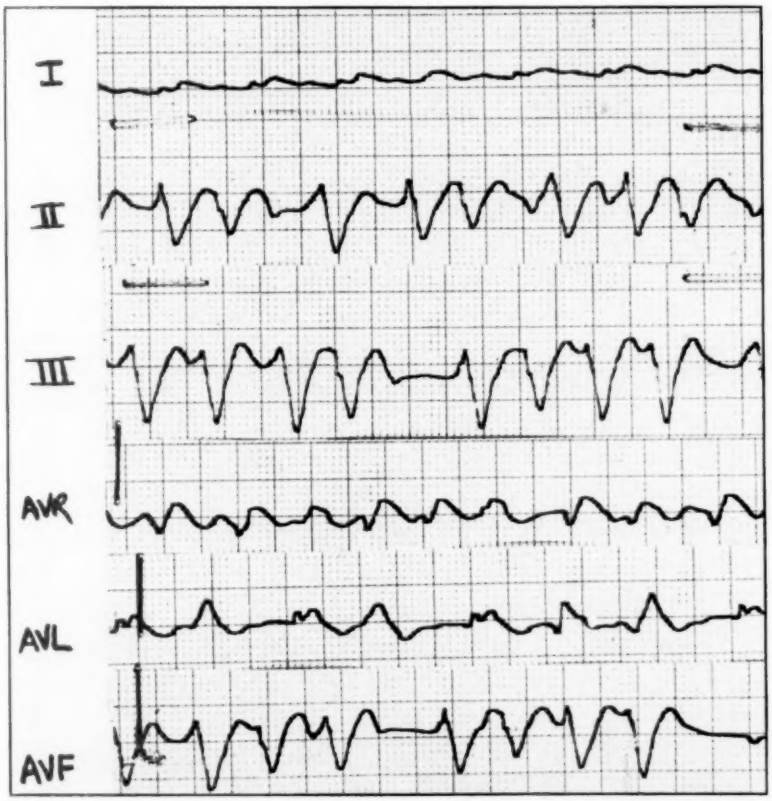

Fig. 3A.—L.L.B., elderly white male with pseudoventricular fibrillation.

We have had the rather worrisome experience of witnessing the inscription of 4 of these pseudoventricular fibrillation disorders and 2 pseudoventricular tachycardias in 6 patients. At slow rates with sinoatrial rhythm

the electrocardiograms of these patients revealed very short P–R intervals (0.12 sec. or less) slurred upstroke of R (delta waves) in standard leads I, II, or III, VL, V1 and V2, or V5 and V6 and slightly broad QRS complexes (at least 0.10 sec. +), left axis deviation of pseudo-bundle branch block, the so-called "Wilson, Wolff, Parkinson, and White Syndrome," or the "Bundle of Kent Syndrome" of Wood and Wolferth or the Accelerated A–V conduction with Pseudo-Bundle Branch Block Syndrome of Wolff and Prinzmetal (Hunter, Papp and Parkinson[3], Knighton[4], Lyle[6], Oehnell[7], Palatucci and Knighton[8], Prinzmetal *et al.*[9], Wolferth and Wood[11], and Wolff, Parkinson and White[13]).

That pseudoventricular fibrillation need not necessarily be associated with the Wolff, Parkinson, White configuration is shown by Fig. 3A, depicting atrial fibrillation superimposed upon complete bundle branch block with top normal A–V conduction. This patient was an elderly male, seen in consultation with Dr. W. C. Goddard.

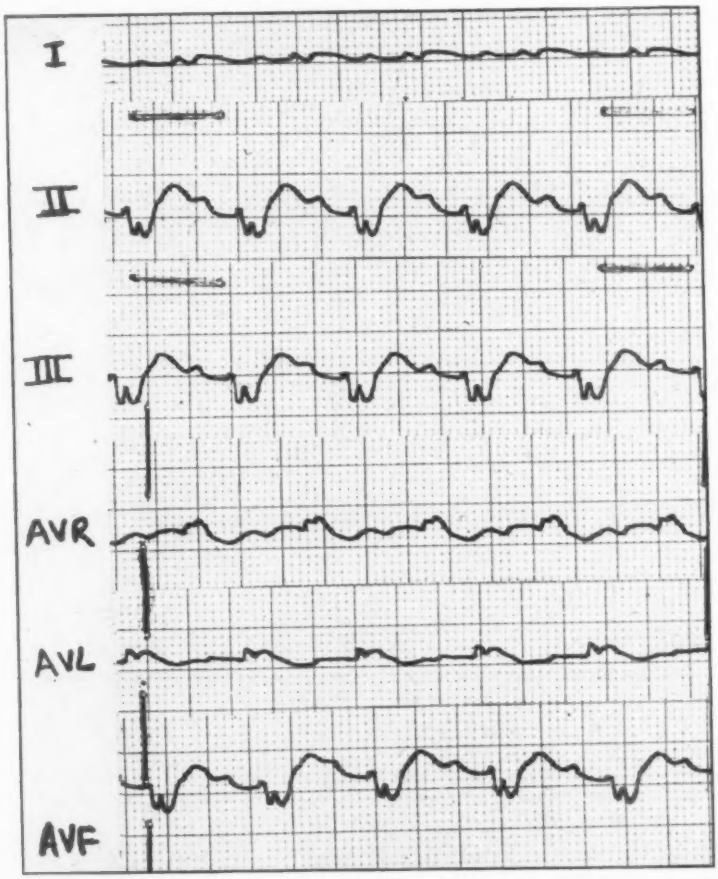

Fig. 3*B*.—L.L.B., after reversion to normal sinus rhythm. Note top normal P–R interval.

Austin, Texas, with myocardial infarction and shock who reverted to normal sinus rhythm, Fig. 3*B*, before death. This is the type of case that ACTH might relieve.

DIAGNOSIS. The correct diagnoses with the favorable prognoses in these cases of high grade tachycardia with bizarre and ominous looking electrocardiograms are suggested by the clinical picture.

The patients with pseudoventricular tachycardia (Dunn, Sarrell and Franklin[1], Fleishman[2], and Levine and Beeson[5]) are not in as severe a shock state and usually do not show acute congestive failure and give no history of a preceding anginal attack. Blood pressure is sustained and "A" and "V" waves may be seen in the jugular venous pulse.

Those with pseudoventricular fibrillation usually have a palpable pulse, audible heart sounds, and a low but obtainable systemic blood pressure and V-waves in the jugular bulb.

The response to procaine amide is usually quite satisfactory although at times large doses, as much as 1 gm. intravenously, are needed.

Electrocardiographic analyses carefully done lead to the correct interpretation. The presence of a perfectly regular rhythm at rates above 200 with P-waves etched on every ventricular complex or on a premature contraction with a broad bizarre QRS before or after a paroxysm, indicates that the rhythm is supraventricular or atrial in origin with pseudoventricular paroxysmal tachycardia.

Absolutely irregular rhythm with bizarre varying ventricular complexes at rates above 200 per minute usually show short periods of narrow complexes with no P-waves and the picture of atrial fibrillation.

Electrocardiograms between attacks show the short P–R interval, slurred upstroke of R (the delta wave), and compensatory lengthening of the QRS, the false bundle branch block picture. This, for some unknown reason, predisposes to paroxysmal atrial tachycardia or fibrillation (Wolff[12]).

MECHANISMS. The characteristic electrocardiographic pattern of a short P–R interval, slurred upstroke of R, and a compensatory broadening of QRS is generally conceded to be due to accelerated conduction of the cardiac excitatory impulse from the atria to a part of the ventricular muscle which is prematurely activated. This is theoretically accomplished through an accessory Bundle of Kent or by a decrease in the normal delay of conduction that occurs in the normal A–V node (Prinzmetal *et al.*[9], Wolferth and Wood[11], and Wood, Wolferth and Geckeler[14]).

Sodi-Pallares found one hyperexcitable focus in the I.V. septum near the pulmonary valve and another near the tricuspid valve (Sodi-Pallares *et al.*[10]). He postulated that patients with Accessory Bundles of Kent ending in one of these two foci would have interference of sinoatrial rhythm by a rhythm of the heterogenic I.V. septal focus. The slurred upstroke of R the delta waves are due to early activation of the hyperirritable point in the I.V. septum.

It should be further stated that the normal A–V pathway is refractory to rates above 240. An irregular ventricular rhythm of 240 or greater, therefore, practically designates the presence of accelerated conduction of the Wilson, Wolff, Parkinson and White type.

TREATMENT. Procaine amide (Pronestyl) in 0.25 to 1.0 gm. doses intravenously seems to us to be the drug of choice. It should be given slowly, intravenously with constant electrocardiographic monitoring and frequent

blood pressure readings as advocated for all I.V. therapy for cardiac mechanism disorders. The drug is stopped after conversion of the disorder has been accomplished or when toxic broadening of the QRS interval increases above 25% of its original width, or if the blood pressure suddenly drops to significantly lower levels.

Quinidine sulphate would seem to be the drug of choice for supraventricular arrhythmias particularly fibrillation. However, it is probably somewhat more dangerous when given intravenously even with monitoring and has caused cardiac standstill.

Both drugs given I.V. may cause equally serious drops in blood pressure and must then be stopped at least temporarily.

If Pronestyl fails, quinidine should be started by mouth in 0.1 gm. doses hourly. Unfortunately these patients often seem to be intolerant of quinidine by mouth during paroxysms. Quinidine is usually well tolerated and fairly effective and preferable as a prophylactic between attacks because procaine amide has more tendency to produce sensitization reactions.

Potassium salts are effective myocardial sedatives also.

Digitalis preparations were used in some of our cases with questionable effects in one case of pseudoventricular paroxysmal tachycardia. It has rarely been found effective, even in lowering the ventricular rate in pseudoventricular paroxysmal fibrillation of atrial fibrillation origin. Increasing the dosage of digitalis in an attempt to slow the ventricles may result in intoxication and may increase the ventricular irritability seriously.

Summary. Patients with accelerated A–V conduction are peculiarly prone to paroxysmal atrial tachycardia and atrial fibrillation.

The development of the paroxysmal atrial disorders gives rise to high ventricular rates with bizarre electrocardiographic tracings which are alarming in simulating serious ventricular mechanism disorders.

The probable mechanism of these pseudoventricular paroxysms has been discussed. The diagnostic criteria have been set forth with emphasis on the presence of a P wave on every complex in the tachycardia and short runs of definitely supraventricular fibrillation with narrow QRS in between the bizarre pseudoventricular runs of complexes. Some of the reported cases of "Ventricular Fibrillation with Recovery" are of this type.

Previously only cases with accelerated AV conduction in the resting tracing have been reported. This series presents a probable rare exception to this rule.

The relatively excellent prognosis of the pseudo-type is emphasized. The relatively prompt and satisfactory response to the relatively safe procaine amide intravenously has been demonstrated.

The importance of taking the clinical picture into consideration in electrocardiographic interpretation is reemphasized.

The clinical axiom follows that the presence of paroxysmal disorders, regular or irregular, with rates above 240 is presumptive evidence of the presence of accelerated A–V conduction as the fundamental cardiac mechanism defect in the patient.

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SUMMARIO IN INTERLINGUA

Rapidissime Arrhythmias e Regular Tachycardias in Paroxysmo in Patientes con e sin Accelerate Conduction Atrio-Ventricular

In patientes con accelerate conduction atrio-ventricular, il ha un tendentia peculiar al disveloppamento de paroxysmal tachycardia atrial e fibrillation atrial.

Le disveloppamento del paroxysmal disordines atrial resulta in alte velocitates ventricular con bizarre configurationes electrocardiographic que es alarmante proque illos simula serie disordines del mechanismo ventricular.

Le mechanismo probabile de iste paroxysmos pseudoventricular es discutite. Le criterios diagnostic es presentate con accentuation del presentia de un unda P in omne complexo in le tachycardia e breve cursos de fibrillation definitemente supraventricular con striction de QRS inter le bizarre cursos pseudoventricular. Certes del reportate casos de "fibrillation ventricular con recuperation" es de iste typo.

Usque al tempore presente, casos de accelerate conduction atrio-ventricular ha essite reportate solmente in registrationes in stato de reposo. Le serie hic reportate representa probabilemente un rar exception de ille regula.

Es sublineate le excellente prognose del typo pseudoventricular. In tal casos, relativemente prompte e satisfacente responsas al relativemente innocente administration intravenose de amido de procaina ha essite demonstrate.

Es signalate de novo le importantia de prender in consideration le tableau clinic in le interpretation de datos electrocardiographic.

Seque como axioma clinic que le presentia de disordines paroxysmal, regular o irregular, con velocitates de plus que 240 constitue un prova presumptive del presentia de accelerate conduction atrio-ventricular como defecto fundamental del mechanismo cardiac in le patiente.

STROPHANTHIN THERAPY IN ATRIAL FLUTTER*

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The therapy of atrial flutter has been a controversial issue since this disturbance was recognized in man by Jolie and Ritchie in 1910. The problem concerns the use of digitalis or quinidine, either separately or in combination. Most observers agree that digitalis is the drug of choice. If given in large doses, digitalis slows the ventricular rate, mainly by increasing vagus tonus and by direct effect on the heart muscle. It tends to convert atrial flutter into atrial fibrillation. This effect of digitalis occurs in the presence or absence of congestive heart failure. Occasionally digitalis will convert atrial flutter to normal sinus rhythm directly or after atrial fibrillation occurs. Quinidine is often used after digitalis has changed flutter to fibrillation to convert the latter to sinus rhythm; it is also used if digitalis fails to influence the flutter at all.

In the present study the cardiac glucoside strophanthin was employed.

Method. The response of 18 patients with 22 single attacks of atrial flutter to strophanthin therapy was studied. The patients were evaluated in an effort to determine the duration of the arrhythmia and the previous use of digitalis therapy. No patient in this study had received digitalis for at least one week prior to the first injection of strophanthin. An electrocardiogram was registered before the injection of strophanthin. Initially strophanthin 0.125 mg. was given intravenously and electrocardiograms were registered immediately after the injection and 5, 10, 15 and 20 minutes after the injection. If there was no evidence of ventricular extrasystoles and the flutter remained unchanged for 24 hours, the dose of strophanthin was increased to 0.25 mg. daily and, in some patients, finally to 0.5 mg. daily. The drug was given until there was a change of the rhythm. If, after 10 days no changes were seen, strophanthin was discontinued and the patient was given oral digitalis or quinidine sulfate. Only strophosid was used.

Patients with paroxysmal flutter of short duration were not treated.

Results. The data obtained are tabulated in Table 1. We were successful in converting atrial flutter to fibrillation in 8 attempts and to normal sinus rhythm in 6. The average duration of intravenous strophanthin therapy before conversion was 5 days. A change of the flutter into normal sinus rhythm occurred as early as the third day of therapy and to atrial fibrillation as early as the second day of therapy. After fibrillation was established the patients were maintained on digitalis leaf.

*This investigation was supported by grants from Hans Petschek, Max Intrator and The Peoples Hospital Foundation.

TABLE 1.—STROPHANTHIN THERAPY IN ATRIAL FLUTTER

Patient	*Age*	*Diagnosis*	*Dosage*	*Number of Days of Strophanthin Therapy*	*Response*
1) P.R.	62	Arteriosclerotic heart disease	0.125 to 0.25 mg.	5	Normal sinus rhythm
2) L.J.	38	Rheumatic heart disease with subacute bacterial endocarditis	"	4	"
			"	4	Therapy interrupted
3) D.S.	59	Hypertensive cardiovascular disease and cerebrovascular accident	"	3	Normal sinus rhythm
4) P.C.	70	Arteriosclerotic heart disease with congestive failure	"	2	Atrial fibrillation
5) M.D.	73	" Syphilis	"	3	Normal sinus rhythm
6) A.W.	68	Hypertensive cardiovascular disease; cerebrovascular accident; pneumonia	0.125 to 0.5 mg.	5	Atrial fibrillation
7) A.R.	90	Arteriosclerotic heart disease	"	5	"
8) J.K.	63	Arteriosclerotic heart disease with congestive failure	"	8	Atrial fibrillation with complete A–V block.
		"	"	8	Nausea, vomiting
9) E.K.	45	Hypertensive cardiovascular disease with congestive failure; flutter diagnosed 2 years	"	8	Normal sinus rhythm
10) E.G.	53	Arteriosclerotic heart disease; diabetes mellitus; syphilis	"	6	Atrial fibrillation
11) J.W.	72	Diabetes mellitus	"	8	Normal sinus rhythm
		Arteriosclerotic heart disease	"	2	Atrial fibrillation
12) J.C.	61	Hypertensive cardiovascular disease with congestive heart failure	"	4	Atrial fibrillation
13) E.F.	80	Arteriosclerotic heart disease with congestive failure; carcinoma of the left breast	0.125 to 0.25 mg.	8	No change
14) M.J.	63	Bronchogenic carcinoma with metastases to the pericardium	"	7	No change

TABLE 1.—STROPHANTHIN THERAPY IN ATRIAL FLUTTER *(Continued)*

Patient	*Age*	*Diagnosis*	*Disease*	*Number of Days of Strophanthin Therapy*	*Response*
15) J.M.	73	Arteriosclerotic heart disease; cerebrovascular accident; diabetes mellitus; flutter diagnosed 3 years before admission and had not responded to therapy	0.125 to 0.5 mg.	7	No change
			"	4	No change
16) L.D.	54	Hypertensive cardiovascular disease with congestive failure	"	7	No change; converted later to atrial fibrillation on digitalis and to normal rhythm on quinidine
17) F.D.	77	Myocardial infarction	"	5	No change
18) G.L.	48	"	"	10	Atrioventricular block increased from 2:1 to 4:1

On 2 occasions it was necessary to repeat the course of strophanthin therapy because of the reversal of atrial fibrillation into flutter; in 2 other instances normal sinus rhythm reverted again into flutter. This occurred probably because the patients discontinued their maintenance dose of oral digitalis.

Six patients did not respond to strophanthin therapy. In this group the diagnoses were myocardial infarction, carcinoma of the breast with metastases, bronchogenic carcinoma with metastases to the pericardium and one with a cerebrovascular accident with a 3-year-old atrial flutter. The 4 patients with the above-named diagnoses expired later during their stay in the hospital but none during or immediately after the strophanthin therapy. The 2 remaining patients in this group did not respond to 7 and 10 days of therapy, respectively. The first patient was later converted to atrial fibrillation on oral digitalis therapy and to normal sinus rhythm on quinidine therapy. The second patient showed increased atrioventricular block (2:1 to 4:1) after 10 days of strophanthin therapy but the flutter persisted.

One patient vomited profusely after the sixth and seventh injection. Subsequently the patient had similar symptoms with maintenance on oral digitalis therapy.

One patient with rheumatic heart disease had 2 episodes of atrial flutter. The first episode converted to normal sinus rhythm after 4 days of strophanthin therapy. The flutter reappeared and a second series of strophanthin injections had to be interrupted since the condition of the patient, who, in the meantime, had developed a subacute bacterial endocarditis, became serious.

Discussion. Strophanthin is still considered dangerous by many physicians because of instances of sudden death during its early usage. This glycoside was initially given in tremendous doses and without adequate control. At times even doses of 10 mg. were given daily while the largest permissible dose is 0.5 mg. This dose is only used if previous injection of smaller doses has not been followed within 30 minutes by extrasystoles. The appearance of ventricular extrasystoles, tachycardias and finally fibrillation are the only risks of strophanthin therapy. This risk is the same if Cedilanid or other preparations of digitalis are injected and can be avoided if the rules mentioned above are followed.

The doses of digitalis necessary to influence atrial flutter are usually large and often initiate unpleasant side effects. This is particularly true in the elderly patient and can make their lives miserable for several weeks. It is known that such side effects are minimal or rare if strophanthin is used. This glucoside has been employed in atrial flutter before by others but no details about its effect in a larger series of cases are available.

Sixty-eight per cent of the cases observed in this study were successfully converted. This percentage of success is even better than that obtained by other authors using different preparations of digitalis glycosides. Actually, White[7] reports that conversion of atrial flutter with digitalis therapy is successful in about half of the patients. Bell and Strong[1] obtained sinus rhythm in 12 out of 29 patients with atrial flutter during digitalis therapy; McMillan and Bellett[4] in 24 out of 43 patients. Parkinson and Bedford[5] studied 20 patients with atrial flutter; in 9 patients sinus rhythm occurred and in 4 patients flutter was converted to fibrillation during administration of digitalis. The authors used strophanthin in 4 patients and recommend this drug only when the symptoms of heart failure make this therapy urgent. Ruede[6] believes that strophanthin is not the glycoside of choice in atrial flutter; "some success" was achieved with it.

Strophanthin dissipates faster and cumulates less than digitalis. It is, therefore, inferior where a sustained effect on atrioventricular conduction is desirable. It has often been stressed that the effect of strophanthin on the ventricular rate in atrial fibrillation is inferior if compared with digitalis because of a smaller increase of vagus tonus. Our results demonstrate that the incidence of conversion of atrial flutter into sinus rhythm or atrial fibrillation compares favorably with the result of digitalis therapy. However, a direct action of strophanthin on the atrial muscle fiber may be involved and the participation of the vagus may be minimal.

Conclusions. The effect of intravenous strophanthin therapy was studied on 18 patients with 22 attacks of atrial flutter.

Conversion of atrial flutter to atrial fibrillation occurred in 8 attacks and to normal sinus rhythm in 6 others. Six patients did not respond to therapy. Four of these died within a few weeks from their underlying noncardiac disease. One patient showed only an increase of the atrioventricular block from 2:1 to 4:1.

There was only one instance of nausea and vomiting and no instance of ectopic rhythm.

Therefore strophanthin is recommended for the conversion of atrial flutter into fibrillation or sinus rhythm.

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SUMMARIO IN INTERLINGUA

Therapia a Strophantina in Flutter Atrial

Le effecto del therapia a strophantina intravenose esseva studiate in 18 patientes con 22 attaccos de flutter atrial.

Le conversion de flutter atrial in fibrillation atrial esseva le resultato in 8 attaccos. In 6 alteres, normal rhythmo sinusal esseva effectuate. Sex patientes non respondeva al therapia usate. Quatro de istes moriva intra alicun septimanas in consequentia de lor subjacente morbo noncardiac. Un patiente manifestava solmente un augmento del bloco atrioventricular ab 2:1 a 4:1.

Il habeva solmente un caso de nausea e vomito e nulle caso de rhythmo ectopic.

Ergo, strophantina es a recommendar pro le conversion de flutter atrial in fibrillation o in rhythmo sinusal.

SUMMARIO IN INTERLINGUA

(See page 155 for original article)

Reactiones Vascular in Hypotension Orthostatic: Observationes con le Hydrogenate Alcaloides Ergotic

Le presente studio esseva executate pro determinar le signification del digital reflexos vasoconstrictive in patientes con hypotension orthostatic debite a un varietate de causas. Es formulate le vista que iste reactiones es de assistentia diagnostic in identificar le causa del hypotension. Le mesuration del pression sanguinee, del velocitate cardiac, del digital reflexos vasoconstrictive, e del volumine de sanguine presentava typic configurationes de reaction. Le hypotension producite per medio del hydrogenate alcaloides ergotic resimilava le hypotension causate per lesiones cerebral.

THE EFFECT OF VENESECTION UPON RENAL FUNCTION OF PATIENTS WITH CONGESTIVE HEART FAILURE

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Although venesection is recognized as being of value in the treatment of congestive heart failure, its mode of action, especially in the production of a sustained beneficial effect, is not fully understood (Fishberg[4]). In normal subjects, phlebotomy or venous congestion of the lower limbs is followed by a decrease in renal blood flow, glomerular filtration rate and excretion of salt and water by the kidney (Lombardo *et al.*[8], Wilkins *et al.*[11]). However, in patients with congestive heart failure, in whom it is well established that the renal circulation is impaired (Merrill[9], Mokotoff, Ross and Leiter[10], Davies and Kilpatrick[1], Fishman *et al.*[5]), similar procedures have been found to produce less consistent changes (Davison and Gaddie[2], Judson *et al.*[7]). In some such patients phlebotomy may actually produce an immediate increase in renal plasma flow, glomerular filtration rate and salt excretion (Judson *et al.*[7]). It is, therefore, possible that venesection may be followed by a sustained increase in the excretion of salt and water and thereby benefit patients with heart failure.

The purpose of the present observations was to determine whether changes in the renal circulation caused by venesection of patients with congestive heart failure were, in fact, accompanied by an improvement in the urinary excretion of sodium and chloride, not only immediately but also in the ensuing 24 hours.

Material and Methods. The observations were made on 10 patients with congestive heart failure. Details of their age, sex and clinical condition are given in Table 1. The procedure was as follows: urine was first collected for a "control" period of 24 hours, at the end of which, between 9 A.M. and 12 M., the immediate effect of venesection on renal function was studied. The glomerular filtration rate (GFR) and renal plasma flow (RPF) were measured before, during and after venesection. Urine was collected for the next 24 hours, after which 2 ml. of a mercurial diuretic† were given by intramuscular injection and another 24-hour urine collection was made.

The patients ate normal meals which contained about 5 gm. of sodium chloride daily, drank as much fluid as they pleased and were confined to bed. Measurements of GFR and RPF were made by the administration of a priming injection in inulin and sodium para-aminohippurate followed by a sustaining infusion. The patients were fasting and semirecumbent during these measurements.

Urine was analyzed for chloride by potentiometric titration and for sodium by flame photometery. Chemical methods for inulin and sodium para-aminohippurate were those previously described by Dick and Davies[3].

Using a similar clearance technique, Davison and Gaddie[2] considered that changes of less than ± 20% in RPF and GFR were within the limits of experimental error.

Results. 1. EFFECT OF VENESECTION ON RENAL CIRCULATION AND URINARY EXCRETION OF SODIUM AND CHLORIDE. Details are given in Table 1 and Fig. 1.

All 10 patients had abnormally low renal plasma flow and all except two, Cases 6 and 10, abnormally low glom-

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†Mersalyl, British Pharmacopeia.

TABLE 1.—THE IMMEDIATE EFFECTS OF VENESECTION UPON THE SYSTEMIC AND RENAL CIRCULATION AND UPON URINARY EXCRETION OF SODIUM AND CHLORIDE OF PATIENTS WITH CONGESTIVE HEART FAILURE

Case	Diagnosis	Sex	Age (yrs.)	Venesection: Amt. (ml.)	Venesection: Time Taken (min.)	J.V.P. (cm. Above Sternal Angle)		B.P. (mm. Hg)	Pulse (per min.)	Ht. (%)	Renal Plasma Flow° (ml./min.)	Glomerular Filtration Rate° (ml./min.)	Filtration Fraction	Urinary Sodium Excretion (μEq./min.)	Urinary Chloride Excretion (μEq./min.)
—	—	—	—	—	—	—	—	—	—	—	600†	130†	0.22†	—	—
1.	M.S., M.I., T.I., A.F.	F	40	680	20	A	15	160/90	98	50	90	42	0.47	8.2	10.2
						B	—	140/70	100	—	96	43	0.45	5.7	14.8
						C	8	135/70	104	43	110	45	0.41	20.8	35.2
2.	C.P.	M	54	665	16	A	9	130/95	122	48	185	69	0.37	10.5	10.1
						B	—	130/95	120	—	184	70	0.38	8.2	11.4
						C	5	125/90	121	46	122	48	0.39	23.1	30.4
3.	C.P.	F	56	580	16	A	10	140/80	104	56	252	78	0.31	11.9	11.9
						B	—	120/70	100	—	242	74	0.30	12.8	6.4
						C	3	125/70	108	49	269	78	0.29	14.1	11.2
4.	C.P.	F	64	650	17	A	8	100/60	90	70	136	44	0.32	—	—
						B	—	100/50	104	—	129	41	0.31	—	—
						C	2	100/50	85	62	140	46	0.33	—	—
5.	C.P., M.I., A.F.	M	67	860	18	A	5	105/75	76	57	280	94	0.33	37.8	23.7
						B	—	105/75	90	—	255	94	0.37	29.4	17.9
						C	0	105/75	88	52	265	85	0.32	20.1	14.4

6.	C.P.	M	30	775	15	A	10	120/90	112	45	337	128	0.38	35.6	81.8
						B	—	120/85	116	—	299	133	0.45	37.8	70.0
						C	4	125/85	112	42	304	120	0.40	35.0	66.0
7.	C.P.	M	66	800	16	A	10	115/70	112	55	167	67	0.40	42.3	44.2
						B	—	110/70	116	—	149	53	0.36	34.4	36.8
						C	5	115/65	108	50	47	23	0.49	10.2	11.1
8.	C.P.	M	46	780	17	A	9	135/95	90	70	154	64	0.42	91.6	65.8
						B	—	120/90	84	—	134	39	0.29	65.1	45.6
						C	6	125/85	84	63	146	54	0.37	96.3	68.5
9.	C.P.	M	55	595	22	A	10	105/60	95	58	158	69	0.44	18.9	16.7
						B	—	120/70	90	—	117	54	0.47	30.4	46.6
						C	3	110/70	88	49	98	47	0.43	31.6	52.5
10.	A.H.D.	M	64	650	19	A	2	175/95	87	51	450	165‡	0.37	136.5	87.0
						B	—	135/75	92	—	317	126	0.41	54.4	39.0
						C	0	140/75	87	49	400	149	0.37	32.1	29.0

M.S. = Mitral Stenosis
M.I. = Mitral Incompetence
T.I. = Tricuspid Incompetence
A.F. = Atrial Fibrillation
C.P. = Cor Pulmonale
A.H.D. = Arteriosclerotic Heart Disease
J.V.P. = Jugular Venous Pressure
B.P. = Blood Pressure
Ht. = Hematocrit

Urine was collected for 5 periods, each of approximately 20 minutes. The figures shown are the averages for the observations made during:
A—the first 2 periods of urine collection (control)
B—the period of venesection
C—the last 2 periods of urine collection (recovery from venesection)
° Not corrected for surface area
† Average values for 4 normal subjects of comparable ages taken from Davies and Kilpatrick[1]
‡ Subsequently re-estimated and a similar value obtained

erular filtration rates compared with those found in normal subjects.

Four patients, Cases 3 to 6, showed no change in the GFR or RPF either during or after venesection. In 2 instances, Cases 1 and 2, the renal circulation did not alter materially during venesection, but afterwards both GFR and RPF fell slightly in Case 2 and the RPF increased in Case 1. In the remaining 4 patients, the GFR and RPF were lowered both during and after venesection; in 2 of these the renal circulation had begun to return towards normal in the postvenesection period.

There was no consistent change in the rate of urinary excretion of sodium and chloride either during venesection or immediately afterwards. There was

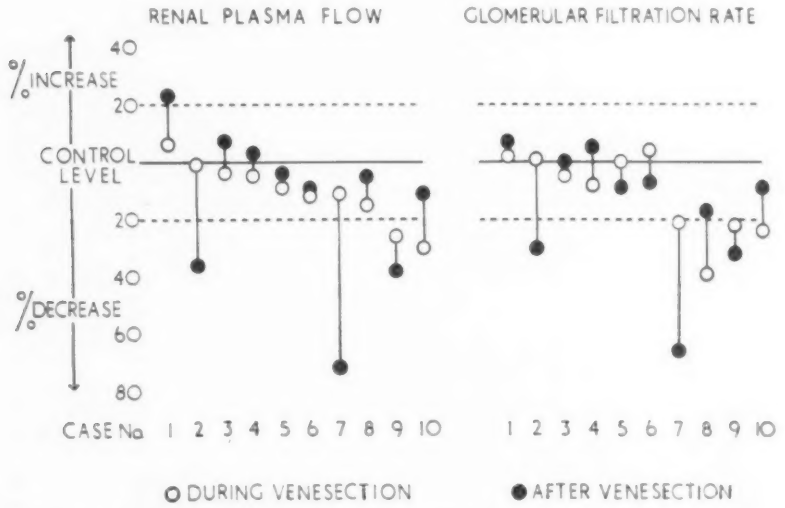

Fig. 1.—Changes in renal plasma flow and glomerular filtration rate during and after venesection, expressed as percentages, compared with the initial control level. The interrupted lines indicate the limits of experimental error.

TABLE 2.—DAILY EXCRETION OF SODIUM AND CHLORIDE BEFORE AND AFTER VENESECTION AND AFTER THE INTRAMUSCULAR INJECTION OF 2 ML. OF MERSALYL OF PATIENTS WITH CONGESTIVE HEART FAILURE

	Sodium (mEq.)			*Chloride (mEq.)*		
Case	*Control*	*After Venesection*	*After Mersalyl*	*Control*	*After Venesection*	*After Mersalyl*
1	3.5	2.0 (— 1.5)	295.0 (+ 291.5)	9.0	6.5 (— 2.5)	314.0 (+ 307.5)
2	1.5	13.0 (+ 11.5)	176.0 (+ 174.5)	7.5	31.0 (+ 23.5)	211.0 (+ 203.5)
3	10.0	4.5 (— 5.5)	98.0 (+ 88.0)	7.0	4.0 (— 3.0)	117.0 (+ 110.0)
6	2.5	16.0 (+ 13.5)	298.0 (+ 295.5)	22.0	30.0 (+ 8.0)	355.0 (+ 333.0)
7	13.0	11.0 (— 2.0)	223.0 (+ 210.0)	35.5	11.0 (—24.5)	239.0 (+ 203.5)
8	38.0	62.5 (+ 24.5)	227.0 (+ 189.0)	34.5	67.5 (+ 33.0)	315.0 (+ 280.5)
9	8.0	30.0 (+ 22.0)	574.0 (+ 566.0)	9.0	42.5 (+ 33.5)	573.0 (+ 564.0)
10	129.0	58.5 (—70.5)	235.0 (+ 106.0)	79.0	57.5 (—21.5)	280.0 (+ 201.0)
Mean	25.7	24.7 (— 1.0)	266.0 (+ 240.0)	25.4	31.2 (+ 5.8)	301.0 (+ 275.0)

+ = increase } compared with control level in twenty-four
— = decrease } hour period before venesection.

also no consistent relationship between the direction of the changes in the renal circulation and urinary electrolyte excretion in individual patients.

2. EFFECT OF VENESECTION AND A MERCURIAL DIURETIC ON SALT EXCRETION. Details are given in Table 2. In comparison with the "control" day, the urinary excretion of sodium and chloride was reduced in 4 patients and increased in the other 4. The average effect on the whole group was a fall of 1 mEq. of sodium, a change well within the limits of experimental error.

In contrast to the small inconsistent change after venesection, the daily urinary excretion of salt showed a very large increase in all patients after the administration of a mercurial diuretic, the average rise being 240 mEq. of sodium.

There was an average loss of weight of 2.0 kg. after the mercurial diuretic and of 0.5 kg. after venesection, which could be accounted for by the weight of blood removed.

3. EFFECT OF VENESECTION ON THE SYSTEMIC CIRCULATION. In all 10 patients venesection produced a fall of venous pressure and of hematocrit. In most patients the pulse rate increased and the blood pressure fell slightly during venesection, the pulse rate decreasing and the blood pressure showing little changes afterwards (Table 1). No patient showed any signs of peripheral circulatory collapse.

Discussion. The present results indicate that in patients with congestive heart failure, venesection has no consistent effect on either the renal circulation or the urinary excretion of sodium and chloride. In patients who did show changes in the renal circulation, these consisted of a moderate fall of glomerular filtration rate and renal plasma flow, and no patient showed the increase in renal circulation observed by Judson *et al.*[7] to accompany venesection of 2 of 5 patients with heart failure. Thus, although the lack of consistent changes in renal circulation after phlebotomy agrees with the findings of Davison and Gaddie[2], and Judson *et al.*[7] in patients with heart failure in whom the circulating blood volume was reduced by venous congestion of the lower limbs, those patients who did show changes responded in the same way as normal subjects who were venesected by Lombardo *et al.*[8].

In the present study there appeared to be little correlation between the changes in renal circulation and the alteration of the urinary sodium and chloride excretion during and after venesection. A similar dissociation between glomerular filtration rate and sodium excretion was also found to accompany venesection of normal subjects, in whom sodium excretion continued to decrease when the glomerular filtration rate was increasing towards its initial level (Lombardo *et al.*[8]). This progressive reduction in salt excretion in the presence of an increasing glomerular filtration rate was seen in only one patient, Case 10, who was probably recovering spontaneously from heart failure with bed rest alone. That no other patient in the present series reacted in this normal manner to an acute reduction in circulating blood volume probably indicated that their kidneys were already retaining salt to the maximum possible extent and no further compensatory effect was possible.

Considered in relation to either the total exchangeable body sodium or the salt content of edema fluid, the absolute changes in urinary salt excretion brought about by venesection were clearly trivial. The largest daily increment of salt excretion observed was 25 mEq. (Table 2), the salt content of approximately one-sixth of a liter of extracellular fluid. Despite the fact

that the patients were given additional water to drink before venesection, the average increase in the daily urinary output of the 8 patients after venesection compared with the "control" period was only one-third of a liter, whereas that after the injection of a mercurial diuretic was 2 L. This was shown by an average loss of weight of 0.5 kg. after venesection and one of nearly 2 kg. after the diuretic. It is, therefore, difficult to attribute the acceptedly beneficial action of venesection to its effect on the urinary excretion of salt and water of patients with heart failure.

All the patients in the present series did, in fact, experience relief of dyspnea for 24 hours after venesection despite the absence of any diuresis. In normal subjects, venesection is followed by an increase in total lung volume and vital capacity (Glaser and McMichael[6]), and one may speculate that the relief of dyspnea of patients with heart failure following venesection results from diminished pulmonary congestion, as suggested by Fishberg[4], and a reduction in the increased rigidity of the lungs which is known to exist in such patients.

Summary. In 10 patients with heart failure venesection produced no consistent change in the renal circulation or urinary excretion of salt. A sustained decrease in salt excretion without a similar change in glomerular filtration rate was seen in only one patient; in the remaining patients renal retention of salt was probably already at the maximum level. This is in marked contrast to the effect of venesection on normal subjects, in whom salt excretion continues to decrease after the renal circulation has started to increase towards its initial level.

In the 24 hours after venesection, the rate of salt excretion remained very low despite small increases in 4 patients. The beneficial effect of venesection in congestive heart failure cannot, therefore, be attributed to its effect on the renal circulation or the urinary excretion of salt.

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(Interlingua on page 206)

THE COUGH RESPONSE OF HEALTHY HUMAN SUBJECTS STIMULATED BY CITRIC ACID AEROSOL

PART II: EVALUATION OF ANTITUSSIVE AGENTS*

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In previous reports (Bickerman *et al.*[1,2]) on the methodology of eliciting a cough response with inhalations of citric acid aerosols, 15 healthy subjects were tested at repeated intervals, once or twice weekly, over a period of 4 to 6 months. By nebulizing a 25% aqueous solution of citric acid in a Vaponefrin nebulizer with oxygen at a flow of 5 liters per minute, each inhalation of the aerosol contained 0.045 mg. of citric acid suspended in a volume of 200 ml. of air. The mean cough response of trained subjects to successive inhalations of citric acid aerosol performed hourly over a 4-hour period indicated a significant degree of reproducibility with respect to the frequency of coughing (number), peak and mean flow rates of the expired gas, volumes exhaled, and the lateral "sound pressures."

Since this method of evoking the cough reflex was noninjurious, simple to perform and yielded a consistent response in the same subject over the 4-hour "dry run" period, a series of agents have been assessed for antitussive activity based upon their alteration of the cough patterns produced by citric acid aerosol using a "double-blind" technique. The results of this evaluation are presented in this report.

Methods. The apparatus employed to elicit cough and the procedure for calibrating this equipment has been described in detail in Part I: Methodology (Bickerman, Cohen and German[2]). A line drawing of the essential components of the apparatus is presented in Fig. 1. Although a 25% solution of citric acid had been employed in the initial study, it became apparent that this concentration of inhaled irritant provided a maximal stimulus for the majority of the subjects tested, and served to reduce the sensitivity of the test. Accord-

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This study has been supported by grants from Hoffmann-La Roche, Inc., Nutley, N.J., Merck & Co., Rahway, N.J., The Upjohn Co., Kalamazoo, Mich., and Eli Lilly and Co., Indianapolis, Ind.

ingly, each of the subjects was challenged with varying concentrations of citric acid arranged in the following order: 1.25%, 2.5%, 5.0%, 7.5%, 10.0%, 15.0%, 20.0% and 25.0%. A "threshold stimulus" level was arbitrarily set at that concentration of citric acid which evoked a total of not less than 4 coughs when inhaled 5 times. Since this "threshold level" varied from subject to subject and occasionally in the same subject from day to day, it was necessary to redetermine this level on each subject prior to a "test run."

indicated, an individual might show variations in sensitivity to the aerosol from one day to the next, in practice, this rarely exceeded one dilution step above or below that level originally determined.

1. PROCEDURE. On the day prior to an antitussive study, subjects were selected who gave no history of a recent upper respiratory infection and presented no evidence of throat irritation or vasomotor rhinitis. A light breakfast was permitted but each individual was cautioned against taking any medication with

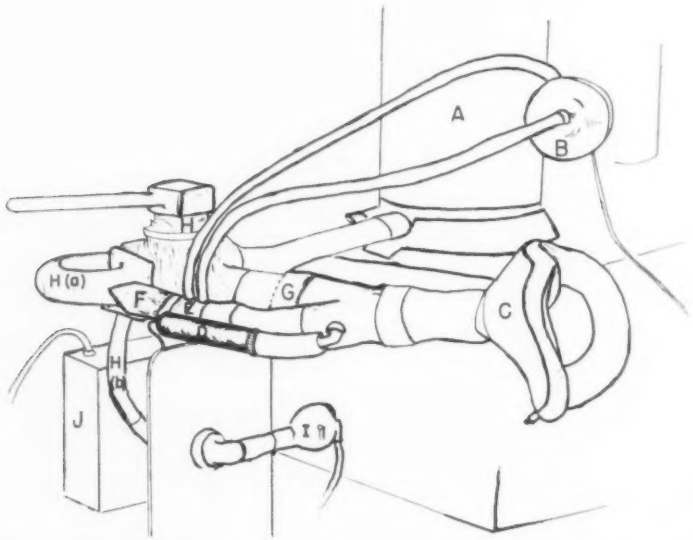


Fig. 1.—Line drawing illustrating the various components consisting of an inspiratory circuit containing a known concentration of citric acid aerosol and an expiratory circuit for recording the cough response. *A*, Ventilometer; *B*, Strain gauge; *C*, Face mask; *D*, Condenser microphone; *E*, Pneumotachograph *F*, Expiratory flutter valve; *G*, Inspiratory Sadd valve; *H*, 4-way valve; (a), main circuit; (b) aerosol circuit; *I*, Nebulizer; *J*, Microphone amplifier. (From Bickerman, H. A., Cohen, B. M., and German, E.: Am. J. Med. Sci., **232**, 57, 1956.)

A total of 19 healthy individuals, 11 males and 8 females consisting of technicians and research fellows, with a mean age of 31 years participated in the study. Fifteen had served as subjects for the first part of the experiment. Four new subjects were recruited over a period of 18 months as replacements for those who left during the course of the study. These replacements were trained in identically the same manner as the original group. In 4 subjects, the "threshold level" remained at the original 25% concentration of citric acid. For the remaining 15, the levels were as follows: 2 at 15%, 6 at 10%, 5 at 5%, 1 at 2.5% and 1 at 1.25%. Although as already

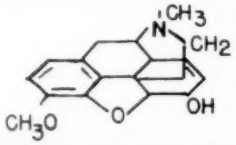
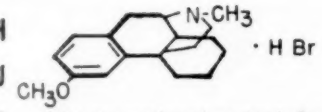
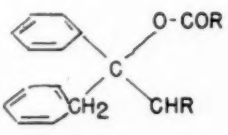
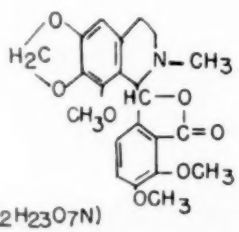
known or suspected antitussive activity. Preceding the study, the respective "threshold levels" of citric acid for each of the subjects to be tested was determined. Each subject was then given 5 inhalations of the appropriate aerosol with a rest period of 1 to 2 minutes between each inhalation. During this rest period, a few sips of water were swallowed to remove any residua of citric acid which might have impinged on the tongue or oropharynx. Immediately after this "control run," the drug to be tested was administered orally and repeat studies were performed at hourly intervals for a period of 4 hours.

Graphic tracings of the cough response

elicited by the aerosol were obtained by means of a spirometer, a pneumotachograph and an Altec condenser microphone which recorded respectively: inspiratory volume and duration, peak and mean flow rates of exhaled air, and the lateral "sound pressure" wave. The frequency or number of coughs per stimulus was readily apparent from either the microphone or pneumotachographic tracings.

2. AGENTS EVALUATED. A "double-blind" technique was employed in which the 18 substances submitted for testing were coded alphabetically and administered to each subject in random sequence as identical white capsules. On decoding these agents at the

TABLE 1.—DRUGS TESTED BY DOUBLE-BLIND TECHNIQUE

Code	Formula	Drug	Dose (mg.)
A		Placebo	—
B			—
E			—
I		Codeine	5
K			15
G			30
H		Romilar	5
J			10
D	(Dextromethorphan Hydrobromide)		20
Q		dl-Propoxyphene	65
O			130
M		d-Propoxyphene	32.5
R	(2-propionoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane hydrochloride)		65
N		l-Propoxyphene	32.5
P			65
V		Narcotine	5
S			15
T			30

$(C_{22}H_{23}O_7N)$

completion of the study, it was learned that all of the drugs except propoxyphene were administered at 3 dosage levels. The various agents together with their dosages and code designations are presented in Table 1.

An average of 8 subjects selected from the pool of 19 trained individuals were tested against each drug. Of these, 6 received all of the coded preparations.

Results. Of the various parameters of the cough response measured, the decrease in the number of coughs and the reduction in the mean flow rate of air exhaled during the act of coughing appeared to offer the most appropriate index for assessing the antitussive properties of the agents tested. The product of these two variables, or the total mean flow rate, of all coughs elicited by each stimulus was employed as a measure of cough intensity.

Data for cough frequency and cough "intensity" were obtained in response to a total of 510 inhalations of citric acid aerosol for the placebo series; 440 for the codeine series; 450 for the dextromethorphan hydrobromide (Romilar) series; 1,010 for the propoxyphene series; and 575 for the narcotine (Nectadon) series. Measurements derived from the graphic tracings of the cough responses elicited by a total of 2,985 inhalations have been subjected to statistical interpretation by use of a 3-factor analysis of variance (Davies[6]) in which the subject, hour and order of stimulus are integrated. Statistical significance has been indicated at the 95% confidence limit about the mean per cent change from the control value for each drug, employing the interaction between subjects and hourly test periods. In comparing the various drugs with one another, the 5% level of significance was also used. Thus, any effect resulting from chance variation alone would occur less than one time in twenty. An illustration of the 3-factor Analysis of Variance for Drug "G" (codeine, 30 mg.) is shown in Table 2. It is apparent that the F-value for the interactions with 30 mg. of codeine exceeds the 1% level of significance indicating that this drug produced a significant reduction in the number of coughs from the control level over the entire 4-hour period.

TABLE 2.—3-FACTOR ANALYSIS OF VARIANCE IN COUGH FREQUENCY FOR DRUG "G" (CODEINE—30 MG.)

	Summary		
Sources of Variation	*Sum of Squares*	*Degrees of Freedom*	*Mean Sum of Squares*
Between Subjects	183.97	5	36.79
Between Hours	20.51	4	5.13
Subjects × Hours	13.75	20	0.69
Residual	32.67	60	
Total	250.90	89	

		F-Values	
Interaction	*F-Value*	$P = 5\%$	$P = 1\%$
Hours/Subjects × Hours	7.43	2.87	4.43

The effect of the various drugs on the frequency of coughing is shown in Table 3. In order to clarify the presentation of these data, all of the coded substances have been grouped according to their pharmaceutical listing. F-values for the 95% level of significance have been converted into a percentile variation about the mean per cent changes for each hourly period.

PLACEBO. It is apparent that none of

TABLE 3.—EFFECT OF ANTITUSSIVE AGENTS ON THE FREQUENCY OF COUGHING ELICITED BY CITRIC ACID AEROSOL IN HEALTHY SUBJECTS

Drug	*No. of Subjects*	*Total Tests Per Hour*	*Cough Interval*	*Mean No. of Coughs*	*Mean % Change*	*Confidence Limits (95%)**
A (Placebo)	8	38	Control	2.67		±31.9
			1 hour	2.47	- 7.5	NS
			2 hours	2.73	+ 2.5	NS
			3 hours	2.80	+ 5.0	NS
			4 hours	3.33	+25.0	NS
B (Placebo)	8	32	Control	2.61		±30.1
			1 hour	2.89	+10.6	NS
			2 hours	2.72	+ 4.3	NS
			3 hours	2.50	- 4.3	NS
			4 hours	2.94	+12.8	NS
E (Placebo)	8	32	Control	3.33		±22.5
			1 hour	3.07	- 8.0	NS
			2 hours	2.93	-12.0	NS
			3 hours	2.93	-12.0	NS
			4 hours	3.40	+ 2.0	NS
I (Codeine) 5 mg.	7	34	Control	2.76		±20.1
			1 hour	2.29	-17.2	NS
			2 hours	2.14	-22.4	S
			3 hours	2.14	-22.4	S
			4 hours	2.29	-17.2	NS
K (Codeine) 15 mg.	6	26	Control	2.22		±20.7
			1 hour	1.50	-32.5	S
			2 hours	1.50	-32.5	S
			3 hours	1.61	-27.5	S
			4 hours	2.00	-10.0	NS
G (Codeine) 30 mg.	6	24	Control	3.22		±17.9
			1 hour	2.17	-32.8	S
			2 hours	1.83	-43.1	S
			3 hours	2.11	-34.5	S
			4 hours	2.50	-22.4	S
H (Romilar) 5 mg.	6	28	Control	2.60		±14.1
			1 hour	1.73	-33.5	S
			2 hours	1.80	-30.8	S
			3 hours	2.13	-18.1	S
			4 hours	2.27	-12.7	NS
J (Romilar) 10 mg.	8	33	Control	2.37		±23.3
			1 hour	1.67	-29.8	S
			2 hours	1.79	-24.6	S
			3 hours	1.79	-24.6	S
			4 hours	1.75	-26.3	S
D (Romilar) 20 mg.	7	29	Control	3.38		±21.7
			1 hour	2.57	-23.9	S
			2 hours	2.52	-25.4	S
			3 hours	2.24	-33.8	S
			4 hours	2.52	-25.4	S

COUGH FREQUENCY (*Continued*)

Drug	*No. of Subjects*	*Total Tests Per Hour*	*Cough Interval*	*Mean No. of Coughs*	*Mean % Change*	*Confidence Limits (95%)**	
Q (Propoxyphene) (dl) - 65 mg.	8	38	Control	2.08		±20.9	
			1 hour	1.96	- 6.0		NS
			2 hours	1.92	- 8.0		NS
			3 hours	1.54	-26.0		S
			4 hours	1.83	-12.0		NS
O (Propoxyphene) (dl) - 130 mg.	8	40	Control	1.97		±13.8	
			1 hour	1.54	-21.7		S
			2 hours	1.40	-29.0		S
			3 hours	1.66	-15.9		S
			4 hours	1.83	- 7.2		NS
M (Propoxyphene) (d) - 32.5 mg.	8	38	Control	2.21		±11.5	
			1 hour	2.04	- 7.5		NS
			2 hours	2.08	- 5.7		NS
			3 hours	2.12	- 3.8		NS
			4 hours	1.96	-11.3		NS
R (Propoxyphene) (d) - 65 mg.	6	28	Control	2.00		±26.1	
			1 hour	1.11	-44.4		S
			2 hours	1.22	-38.9		S
			3 hours	1.67	-16.7		NS
			4 hours	1.50	-25.0		NS
N (Propoxyphene) (l) - 32.5 mg.	7	28	Control	2.00		±23.8	
			1 hour	1.44	-27.8		S
			2 hours	1.56	-22.3		NS
			3 hours	1.44	-27.8		S
			4 hours	1.72	-13.9		NS
P (Propoxyphene) (l) - 65 mg.	6	30	Control	2.10		±24.5	
			1 hour	1.40	-33.3		S
			2 hours	1.43	-31.7		S
			3 hours	1.37	-34.9		S
			4 hours	1.70	-19.0		NS
V (Narcotine) 5 mg.	6	30	Control	1.57		±21.2	
			1 hours	1.07	-31.9		S
			2 hours	1.27	-19.1		NS
			3 hours	1.27	-19.1		NS
			4 hours	1.47	- 6.4		NS
S (Narcotine) 15 mg.	7	35	Control	1.71		±16.7	
			1 hour	1.20	-30.0		S
			2 hours	1.43	-16.7		S
			3 hours	1.31	-23.3		S
			4 hours	1.37	-20.0		S
T (Narcotine) 30 mg.	10	50	Control	1.72		±25.0	
			1 hour	1.11	-35.5		S
			2 hours	1.04	-39.5		S
			3 hours	1.18	-31.4		S
			4 hours	1.26	-26.7		S

*Three-Factor Analysis of Variance (Subject-Hour-Order) Expressed as 95% Limit.

the placebos, A, B or E, show any suppression in the frequency of coughing over the 4 hours tested.

CODEINE. Although the 5-mg. dose was barely significant at the 5% level for the second and third hours only, 15 mg. was an effective antitussive for the first 3 hours, and 30 mg. over a period of 4 hours.

DEXTROMETHORPHAN HYDROBROMIDE (ROMILAR). At a dose of 5 mg., Romilar showed significant cough suppression for the first 3 hours. Both the 10- and 20-mg. doses were effective over the 4 hours tested.

PROPOXYPHENE. Some inconsistencies in response to this series of compounds were noted. While a significant antitussive effect was observed at the third hour for 65 mg. of *dl*-propoxyphene and for the first 3 hours for the 130-mg. dose, the mean per cent changes from the control were less marked than with the other drugs tested. The 32.5-mg. dose of the dextro- compound exhibited no significant antitussive activity. Twice this dose, however, was effective for the first 2 hours. Both 32.5 and 65 mg. of levo-propoxyphene showed significant effects for a period of three hours.

NARCOTINE (NECTADON). While 5 mg. of narcotine exhibited an antitussive effect at the first hour only, both 15 and 30 mg. showed significant activity over the 4-hour test period.

In general, the effect of these agents on the total mean flow rates of gas exhaled during coughing paralleled the changes in cough frequency. This is illustrated in Table 4. The only major discrepancy noted was in the response to Romilar 20 mg. which appeared to be insignificant except for the third-hour period. This will be discussed later.

In addition to evaluating the antitussive properties of these agents, comparisons between different dosage levels of the same drug and between the various drugs themselves were of interest. Since the dosage levels for each drug differed and variations in the weight of the subjects tested did not permit adjustment on a milligram per kilogram body weight basis, it was difficult to quantitate significant differences in activity between the four effective agents. In assessing antitussive activity, duration of cough suppression following a single dose must be considered as well as the degree of inhibition.

The simplest way to compare these drugs for effectiveness over the entire 4-hour period was to plot the per cent decrease in the number of coughs from the control level for each dose of the drug using the combined mean of the 4 hourly periods. Of the propoxyphene series, only the levo- form representing the most active compound of this group was plotted. The three placebos were grouped to serve as the inactive control while the three dosage levels of codeine represented active controls. This is illustrated in Fig. 2.

Qualitatively, a dose-response relationship is apparent for each of the drugs tested. In comparing these agents against codeine, 10 mg. of Romilar appeared to coincide with 15 mg. of codeine in antitussive activity. Although 20 mg. of Romilar had an effect between that of 15 and 30 mg. of codeine, there was no significant difference between this dose and the 10 mg. level. The 5-mg. dose of narcotine corresponded to 5 mg. of codeine and 30 mg. had the same cough suppressing activity as a similar dose of codeine. L-propoxyphene, 32.5 mg. had an antitussive effect ranging between 5 and 15 mg. of codeine, with the 65-mg. dose falling between 15 and 30 mg. of codeine. When subjected to variance analyses, overlap at the 5% level occurred with all four agents so that

TABLE 4.—EFFECT OF ANTITUSSIVE AGENTS ON THE TOTAL MEAN FLOW RATE OF AIR EXHALED DURING COUGHING

Drug	*No. of Subjects*	*Total Tests Per Hour*	*Cough Interval*	*Total Mean Flow (L./sec.)*	*Mean % Change*	*Confidence Limits (95%)**
A (Placebo)	8	38	Control	3.83		±37.4
			1 hour	4.01	+ 4.7	NS
			2 hours	4.45	+16.4	NS
			3 hours	4.56	+19.2	NS
			4 hours	5.11	+33.6	NS
B (Placebo)	8	32	Control	3.56		±29.2
			1 hour	4.30	+20.9	NS
			2 hours	3.99	+12.2	NS
			3 hours	3.79	+ 6.7	NS
			4 hours	3.72	+ 4.5	NS
E (Placebo)	8	32	Control	4.63		±31.6
			1 hour	5.45	+17.9	NS
			2 hours	5.07	+ 9.7	NS
			3 hours	4.42	- 4.5	NS
			4 hours	5.50	+18.9	NS
I (Codeine) 5 mg.	7	34	Control	5.31		±18.8
			1 hour	4.53	-14.6	NS
			2 hours	3.79	-28.5	S
			3 hours	3.94	-25.8	S
			4 hours	3.63	-31.5	S
K (Codeine) 15 mg.	6	26	Control	4.41		±22.1
			1 hour	3.16	-28.5	S
			2 hours	2.83	-35.8	S
			3 hours	3.31	-24.9	S
			4 hours	4.01	- 9.2	NS
G (Codeine) 30 mg.	6	24	Control	5.29		±21.8
			1 hour	4.07	-23.0	S
			2 hours	3.24	-38.8	S
			3 hours	3.68	-30.1	S
			4 hours	3.69	-30.3	S
H (Romilar) 5 mg.	6	28	Control	4.63		±19.6
			1 hour	3.28	-29.2	S
			2 hours	3.29	-28.9	S
			3 hours	3.91	-15.6	NS
			4 hours	4.27	- 7.1	NS
J (Romilar) 10 mg.	8	33	Control	4.17		±20.5
			1 hour	2.92	-30.0	S
			2 hours	3.16	-24.3	S
			3 hours	2.94	-29.6	S
			4 hours	2.99	-28.3	S
D (Romilar) 20 mg.	7	29	Control	4.78		±25.7
			1 hour	4.40	- 7.9	NS
			2 hours	3.86	-19.2	NS
			3 hours	3.34	-30.1	S
			4 hours	4.05	-15.3	NS

*Three-Factor Analysis of Variance (Subject-Hour-Order) Expressed as 95% Limit.

TOTAL MEAN FLOW DURING COUGHING (*Continued*)

Drug	No. of Subjects	Total Tests Per Hour	Cough Interval	Total Mean Flow (L./sec.)	Mean % Change	Confidence Limits (95%)*
Q (Propoxyphene) (dl) 65 mg.	8	38	Control	4.08		±20.6
			1 hour	3.98	- 2.5	NS
			2 hours	3.61	-11.4	NS
			3 hours	3.06	-24.9	S
			4 hours	3.56	-12.8	NS
O (Propoxyphene) (dl) 130 mg.)	8	40	Control	4.46		±16.6
			1 hour	3.43	-23.1	S
			2 hours	3.18	-28.6	S
			3 hours	3.68	-17.5	S
			4 hours	4.07	- 8.7	NS
M (Propoxyphene) (d) - 32.5 mg.	8	38	Control	3.94		±18.5
			1 hour	3.91	- 0.8	NS
			2 hours	4.08	+ 3.5	NS
			3 hours	4.05	+ 2.6	NS
			4 hours	3.64	- 7.7	NS
R (Propoxyphene) (d) - 65 mg.	6	28	Control	4.19		±28.3
			1 hour	2.78	-29.1	S
			2 hours	2.80	-28.7	S
			3 hours	3.38	-16.9	NS
			4 hours	3.55	-13.4	NS
N (Propoxyphene) (l) - 32.5 mg.	7	28	Control	4.23		±19.5
			1 hour	3.00	-28.9	S
			2 hours	3.28	-22.3	S
			3 hours	2.88	-31.8	S
			4 hours	3.60	-14.8	NS
P (Propoxyphene) (l) - 65 mg.	6	30	Control	4.10		±23.2
			1 hour	2.92	-28.7	S
			2 hours	2.68	-34.6	S
			3 hours	2.64	-35.7	S
			4 hours	2.99	-27.0	S
V (Narcotine) 5 mg.	6	30	Control	2.71		±22.9
			1 hour	1.88	-30.6	S
			2 hours	2.09	-22.9	S
			3 hours	2.11	-22.1	NS
			4 hours	2.60	- 4.1	NS
S (Narcotine) 15 mg.	7	35	Control	3.68		±15.1
			1 hour	2.62	-28.9	S
			2 hours	2.99	-18.7	S
			3 hours	2.59	-29.5	S
			4 hours	2.63	-28.5	S
T (Narcotine) 30 mg.	10	50	Control	3.68		±19.7
			1 hour	2.45	-33.4	S
			2 hours	2.28	-33.8	S
			3 hours	2.48	-32.6	S
			4 hours	2.57	-30.2	S

no significant discriminations could be made between these antitussives.

The per cent changes in cough frequency at each hourly period was plotted for the placebo group, codeine and narcotine at 30 mg., Romilar at the 20-mg. level, and *l*-propoxyphene at 65 mg. This is shown graphically in

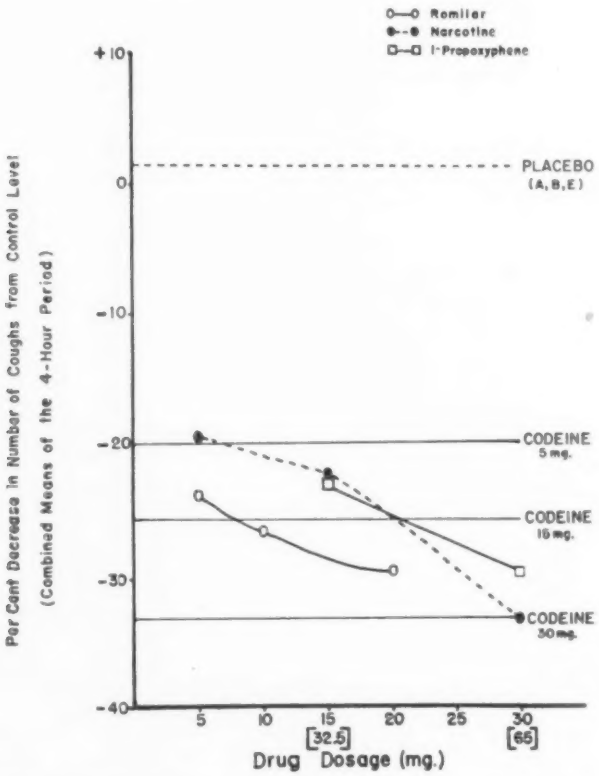


Fig. 2.—Antitussive activity of Romilar, narcotine and *l*-propoxyphene compared with placebo and codeine based upon the per cent decrease in cough frequency from the control level over the entire 4-hour period.

placebo series showed a slight increase of +3.9% from the control level.

Although all of the agents at these dosages exhibited a significant decrease in cough frequency from the control level as compared with the placebos, there were slight but apparent differences in the time interval for peak effect. The effectiveness of codeine and narcotine were maximal at the second hour, whereas the peak drop with Romilar and *l*-propoxyphene occurred at the third hour.

Fig. 3. Using the combined means of the 3 placebos for each hourly period, it would appear that the number of coughs increased at the fourth hour by 13%. When this was corrected by excluding one subject, E.H., who had paroxysmal coughing at the fourth hour, the combined mean for the

Although the method of study was such that only a single dose of a drug was given to a subject on any one day,

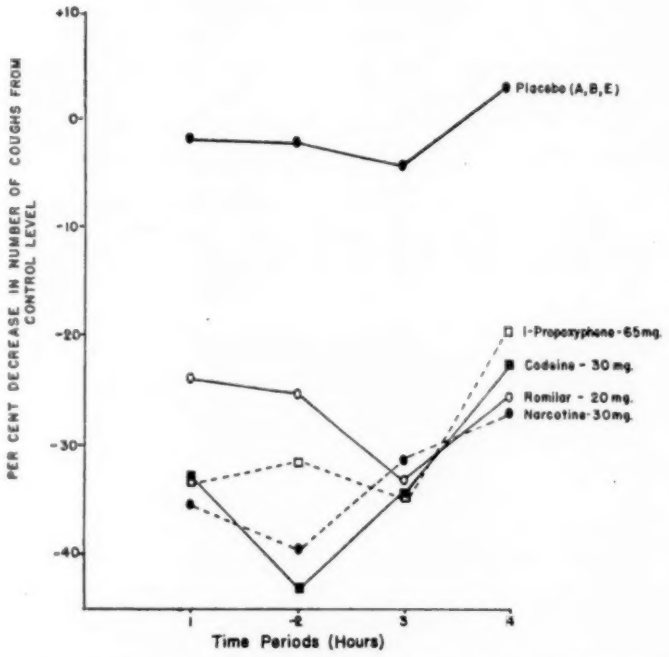


Fig. 3.—Effect of antitussive agents on the number of coughs expressed as a mean per cent change at each hourly period from the control value.

TABLE 5.—SIDE EFFECTS NOTED FOLLOWING ADMINISTRATION OF SINGLE DOSES OF ANTITUSSIVE AGENTS

	Side Effects (Number of Subjects)*					
Drug	*Slight Nausea*	*Slight Headache*	*Slight Drowsiness*	*"Light-Headed"*	*Dryness*	*Totals*
Placebo (A, B, E)	1	0	0	0	0	1
Codeine— 5 mg.	0	0	0	1	0	1
15 mg.	0	1	0	0	2	3
30 mg.	1	0	1	3	2	7
Romilar— 5 mg.	0	0	1	0	0	1
10 mg.	0	0	1	1	0	2
20 mg.	1	0	1	0	0	2
dl-Propoxyphene,						
65 mg.	0	0	0	1	0	1
130 mg.	0	1	0	1	0	2
d-Propoxyphene						
32.5 mg.	0	0	0	0	0	0
65.0 mg.	1	0	0	2	0	3
l-Propoxyphene						
32.5 mg.	0	0	0	2	1	3
65.0 mg.	0	1	0	1	1	3
Narcotine— 5 mg.	0	0	0	1	0	1
15 mg.	1	0	0	0	0	1
30 mg.	0	0	2	1	0	3

* Reported by 8 of the 19 subjects tested.

voluntary remarks by the subjects concerning side effects is shown in Table 5. It was of interest that only 8 of the 19 subjects reported any unusual reactions. While these were all stated as being "slight" or "minor" in character, the same type of reaction was often reported by the same individual when retested against a given preparation. The incidence of side effects reported for 30 mg. of codeine was considerably greater than for the other drugs tested.

Discussion. A review of the literature on the evaluation of antitussive agents discloses that the majority of the reports are concerned with clinical appraisals in patients suffering from disease entities associated with chronic cough. Among these are the excellent papers of Cass and Frederik[3,4,5] who have made quantitative evaluations based on multiple observation periods and an elaborate scoring method. Since 1938, when Ernst[7] first described

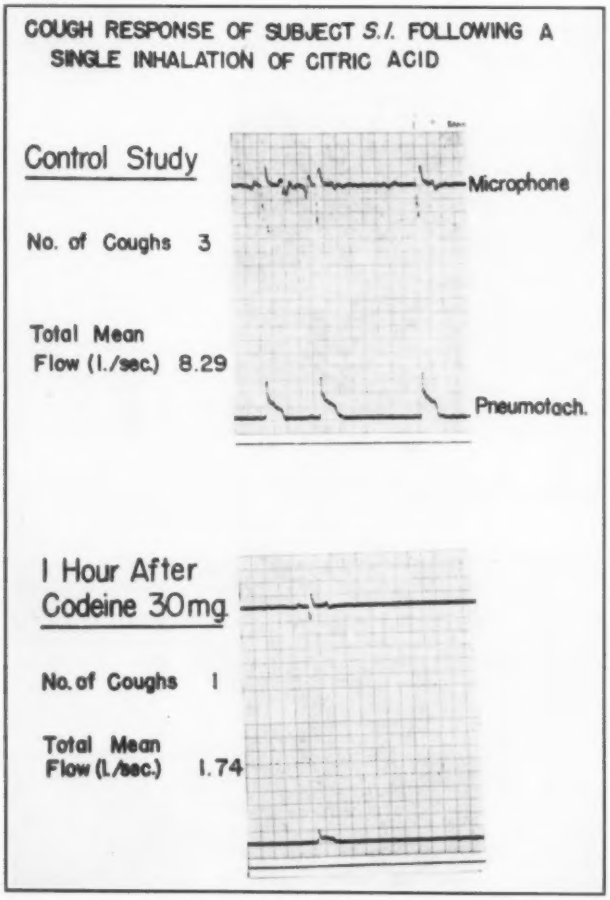

COUGH RESPONSE OF SUBJECT S.I. FOLLOWING A SINGLE INHALATION OF CITRIC ACID
Control Study
No. of Coughs 3
Total Mean Flow (l./sec.) 8.29
Microphone
Pneumotach.
1 Hour After Codeine 30mg.
No. of Coughs 1
Total Mean Flow (l./sec.) 1.74

Fig. 4.—Graphic tracings of the cough response of Subject S.I. following a single inhalation of citric acid. Comparison of the control study with codeine, 30 mg. one hour after ingestion, showing decrease in both frequency and intensity.

an experimental technique for eliciting cough, a total of 20 reports on this method of assessing antitussive activity have been published. Many of these experimental methods have been reviewed by Tiffeneau[8]. Of these, only 7 papers pertain to studies on human subjects. In general, experimental

mates the natural cough occurring with respiratory tract infection in which irritation due to inflammatory changes and the presence of retained secretions serve to initiate the cough reflex.

In addition to the actual number of coughs, it was felt that other variables of the cough response would

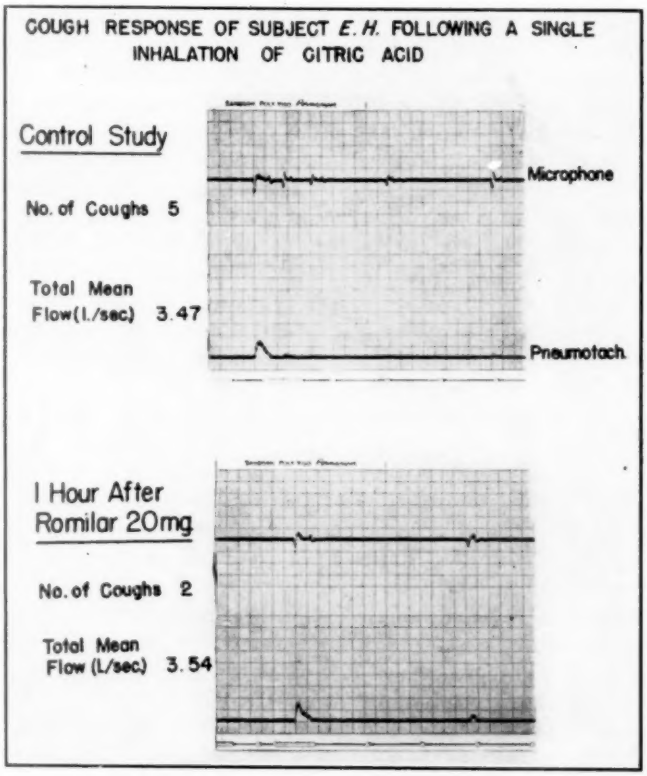

COUGH RESPONSE OF SUBJECT E. H. FOLLOWING A SINGLE INHALATION OF CITRIC ACID
Control Study
No. of Coughs 5
Total Mean Flow(l./sec) 3.47
Microphone
Pneumotach
1 Hour After Romilar 20mg
No. of Coughs 2
Total Mean Flow (L/sec) 3.54

Fig. 5.—Comparison of the cough response of Subject E. H. following a single inhalation of citric acid before and one hour after Romilar 20 mg., illustrating a decrease in frequency without alteration of intensity of cough.

coughing has been produced by mechanical or chemical irritants. It was felt that the cough response elicited by the inhalation of citric acid aerosol resulted from the stimulation of both chemical and mechanical receptors in the tracheobronchial passageway. Physiologically, this approxi-

yield more sensitive criteria for the assessment of antitussive activity. Although, for the most part, there was good agreement between the measurements of cough frequency and total mean flow rate in the data presented, it was interesting to note that our subjects gave two types of response fol-

lowing the administration of an effective antitussive. The more common response was one in which both cough frequency and volume flow rates were reduced. This is illustrated in Fig. 4, for Subject S.I. on codeine, 30 mg. An atypical pattern of response is shown in Fig. 5, for Subject E.H. on Romilar, 20 mg., in which the number of coughs are reduced but the remaining cough or coughs are characterized by insignificant changes in the total mean flow rate. Although this happens to be an illustration with Romilar, similar responses were encountered with other agents.

Justification for the use of other variables in measuring the cough response depends in large part upon a more precise definition of what is meant by the term *antitussive activity*. It is apparent that in addition to a reduction in the frequency of coughing, the change in intensity or effort associated with coughing may be of equal importance. While the data presented are derived from experimental coughs elicited by an inhaled irritant, the graphic tracings indicate that some subjects may respond to an antitussive with a decrease only in the number of coughs while other subjects may have a reduction in both number and intensity. In each instance, the patient's subjective response would confirm the effectiveness of the antitussive agent. From the physiologic point of view, coughing represents perhaps the most effective mechanism for ridding the airway of retained secretions. In the presence of such secretions, the ideal antitussive might well be one which, although reducing the number of ineffective coughs, permits an adequate flow rate in the remaining coughs so as to aid bronchial drainage. In the absence of secretions, when cough is purely irritative or reflex in character, a decrease in the frequency of coughing as well as the intensity would be desirable. This is in keeping with the clinical impression that patients often state that they are benefited by an antitussive drug even though it is obvious to the physician that some cough persists. The quantitative measurement of those variables associated with the intensity of cough play an important role in the over-all assessment of these drugs.

Summary and Conclusions. A "double-blind" study was performed to evaluate the antitussive activity of various dosage levels of dextromethorphan hydrobromide (Romilar), narcotine (Nectadon), propoxyphene, codeine and placebo. The 18 coded preparations were administered in random fashion to 19 trained, healthy subjects in whom cough was elicited experimentally by the inhalation of a known amount of citric acid aerosol.

Graphic tracings of the cough response were obtained by recording systems employing a spirometer, a pneumotachograph and an Altec condenser microphone. Following an initial control study consisting of 5 inhalations of citric acid aerosol, a capsule containing the antitussive agent was administered orally and the subject retested at hourly intervals for a period of 4 hours. The data derived from the tracings of the cough responses elicited by a total of 2,985 inhalations of aerosol were subjected to statistical analyses. Of the four variables of the cough response measured, only cough frequency and the total mean flow rate of each cough (intensity factor) have been employed in evaluating antitussive activity.

The results of this study indicate that: 1) codeine, Romilar, *l*-propoxyphene and narcotine are significantly more effective antitussives than placebo.

2) There were no statistical differ-

ences in the activity of Romilar, 10 mg., narcotine, 15 mg., and *l*-propoxyphene 32.5 mg. when compared with codeine, 15 mg.

3) Good dose-response curves were obtained with all the preparations when data for cough frequency were plotted. The occasional dissociation between the frequency response and the total mean flow rates is discussed.

4) Antitussive activity of the effective agents tested at the highest dosage level appeared to persist over the 4-hour period.

This study indicates the feasibility of employing experimental cough induced by citric acid aerosol as a quantitative method for assessing antitussive activity. Other variables of the cough response elicited in this manner may yield additional information when subjected to analysis. Furthermore, it would appear desirable to combine the experimental approach with clinical studies by applying this method to patients with coughing due to disease states.

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SUMMARIO IN INTERLINGUA

Responsa de Tusse a Aerosol de Acido Citric in Normal Subjectos Human Parte II: Evalutation de Agentes Anti-Tusse

Un "duple-occulte" studio esseva facite pro evalutar le action anti-tusse de varie nivellos de dosage de hydrobromuro de dextromethorphano (Romilar), narcotina (Nectadon), propoxypheno, codeina, e un medication fictitie. Le 18 preparatos usate esseva identificate per cifras e administrate al hasardo a 19 experientiate subjectos normal in qui tusse esseva provocate experimentalmente per le inhalation de cognoscite quantitates de aerosol de acido citric.

Graphicos del responsa de tusse esseva obtenite per apparaturas de registration consistente de un spirometro, un pneumotachographo, e un microphono a condensator typo Altec. Post un studio de controlo initial que consisteva de 5 inhalationes de aerosol de acido citric, un capsula continente le agente anti-tusse esseva administrate oralmente, a le subjecto esseva retestate a intervallos de un hora durante un periodo de 4 horas. Le datos obtenite ab le registrationes del responsas de tusse post un total de 2.985 inhalationes de aerosol esseva subjicite a analyses statistic. Inter le quatro variabiles del responsa de tusse mesurate, solmente le frequentia de tusse e le total fluxo medie del tusses individual (le factor de intensitate) esseva usate in evalutar le action anti-tusse.

Le resultatos de iste studio indica: (1) Codeina, Romilar, *l*-propoxypheno, e narcotina es significativemente plus efficace como agentes anti-tusse que le medication fictitie. (2) Esseva constatate nulle differentias statistic in le activitate

de Romilar (10 mg), narcotina (15 mg), e *l*-propoxypheno (32,5 mg) in comparation con codeina (15 mg). (3) Bon curvas del responsa como function del dose esseva obtenite in le caso de omne le preparatos quando le responsa esseva representate per le frequentia de tusse. Le occurrentia sporadic de dissociation inter le responsa de frequentia e le responsa del factor de intensitate es discutite. (4) Le action anti-tusse del agentes efficace testate al plus alte nivello de dosage pareva persister durante le integre periodo de 4 horas.

Iste studio demonstra le practicabilitate de usar tusse de induction experimental per aerosol de acido citric in evalutar quantitativemente le action anti-tusse de un date preparato. Altere variabiles del responsa de tusse provocate in iste maniera va possibilemente resultar in informationes additional quando illos es subjicite al analyse statistic. In plus, il pare desirabile combinar le methodologia experimental con studios clinic per applicar le hic-presentate systema a patientes con tusse como symptoma de statos pathologic.

SUMMARIO IN INTERLINGUA

(See page 185 for original article)

Le Effecto de Venesection Super le Function Renal de Patientes con Congestive Disfallimento Cardiac

In 10 patientes con disfallimento cardiac, venesection produceva nulle uniforme alteration del circulation renal o del excretion urinari de sal. Un continue reduction del excretion de sal sin correspondente alterationes del tempo de filtration glomerular esseva constatate in solmente un patiente. In le altere patientes, le retention renal de sal esseva probabilemente jam a su nivello maximal. Isto forma un contrasto marcate con le effecto de venesection in subjectos normal, in qui le excretion de sal continua decrescer post que le circulation renal ha comenciate montar verso su nivello initial.

Durante le prime 24 horas post le venesection, le excretion de sal remaneva multo lente, ben que parve augmentos esseva notate in 4 casos. Le effecto benefic de venesection in congestive disfallimento cardiac non pote, per consequente, esser attribuite a su effecto super le circulation renal o super le excretion urinari de sal.

A RESIN COMPLEX FOR PROLONGED ANTITUSSIVE EFFECTS

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While there has been an increasing acceptance of oral therapeutic preparations designed to produce a full control of a variety of clinical syndromes by means of sustained release of useful drugs over a period of 6 or more hours, this principle has not been used in the preparation of a satisfactory, therapeutically effective antitussive preparation.

Most long-acting, sustained-release products now available depend upon the principle of the dissolution of variously sized, enteric-coated granules, making their respective drug loads available at different times. Experience has proven that such a means of delaying the release of drugs is unpredictable in that the time required for dissolving or extracting the drug from the granule mass varies considerably from individual to individual, and from hour to hour in the same individual, depending mainly upon the state of the digestive fluids in the gastrointestinal tract. In order to overcome this disadvantage a totally new approach to the sustained release of drugs has been developed utilizing the principle of ionic exchange under conditions whereby the active drug is released at a predictable rate in the presence of the ions of the gastrointestinal tract irrespective of the location of the drug complex (Freed, Keating and Hays[2]).

Since the truly effective antitussive agents belong to the codeine family, it is desirable to utilize a means of potentiating small doses of one of these derivatives in order that the habit-forming potential would be kept at an absolute minimum. Dihydrocodeinone is the antitussive of choice in that Curtis and Browning[1] and Hyman and Roseblum[3] in extensive studies have shown it not only to be exceedingly effective in the relief of cough, but state that it does not cause significant retention of sputum, does not interfere with expectoration and is singularly free from undesirable side effects, particularly the constipation which is frequently encountered when codeine is used. Keeping the above in mind, a product which combines both the efficiency of predictable, sustained ionic release and the potentiation of the codeine derivative has been developed and is described here.

Materials and Methods. Anion and cation exchange resins form reversible complexes with organic acids and bases. Dissociation of these complexes proceeds at a finite rate. If the proper ion exchange resin is chosen with properties appropriate for the drug under consideration, this rate of dissociation can be controlled to produce a uniform release of the therapeutic agent. This release is solely dependent upon the availability of ions, and since the total concentration of positive or negative ions in the gastrointestinal fluid varies within relatively narrow limits, the rate of the exchange of ions for the drug is relatively constant. A mixture of dihydro-

codeinone-phenyltoloxamine-resin-complex has such properties.* Table 1 illustrates the rate of release of dihydrocodeinone from a sample of this product when the dissociation is studied *in vitro* utilizing concentrations of hydrogen and alkali-salt cations approximating those found in succession in the gastrointestinal tract. The resin-complex is percolated with successive portions of simulated gastric or intestinal juice at a rate of 50 ml. per hour, and the amount of drug released measured spectrophotometrically.

It will be noted that approximately 76% of the total dihydrocodeinone in the complex is released in an 8-hr. period. Little additional dihydrocodeinone is released after 12 hr. in the alkaline medium approximating the cation concentrations found in the intestine. It would appear from the uniformity of the *in vitro* release of the drug over the 8-hr. period that 'Tussionex' should have a sustained antitussive effect.

TABLE 1.—*IN VITRO* RELEASE OF DIHYDROCODEINONE AND PHENYLTOLOXAMINE

Hour	*Elution Solution Used*	*Mg. of Drug Released from One Dose*	
		Dihydrocodeinone	*Phenyltoloxamine*
1	Simulated Gastric Juice (less enzymes)	.4	.6
2	" " "	.3	.5
3	" " "	.3	.6
4	Simulated Intestinal Juice (less enzymes)	.5	.7
5	" " "	.8	.8
6	" " "	.6	.8
7	" " "	.5	.4
8	" " "	.4	.3

Results. IN ANIMALS. The *in vitro* sustained release of dihydrocodeinone--resin-complex was confirmed in animals by means of a study in dogs utilizing the method of Winter and Flataker[4,5]. Figure 1 shows the average responses of groups of 4 or more animals when given oral doses of codeine, dihydrocodeine, dihydrocodeinone, dihydrocodeinone-resin-complex and dihydrocodeinone-phenyltoloxamine-resin-complex. It will be noted that the commonly accepted 6 to 1 ratio of antitussive activity between dihydrocodeinone and codeine is borne out in this experiment. It will also be noted that the same dose of dihydrocodeinone (.37 mg./kg.) when administered as the resin-complex, produces a greater depth of suppression, and the effect lasts a substantially longer period of time.

During the course of the animal studies, it was discovered that the addition of small amounts of certain antihistaminics potentiated the depth of the cough suppression, and when the antihistaminic, phenyltoloxamine, was added as a sustained-release resin-complex† a true potentiation of the antitussive activity was obtained and is shown as curve V in Fig. 1.

As a result of the combination of potentiation of the antitussive effect by the antihistaminic-resin-complex and the increased antitussive activity of the dihydrocodeinone-resin-complex over dihydrocodeinone bitartrate, it was predicted that the resulting com-

*Tussionex is the R. J. Strasenburgh Company trademark for a brand of dihydrocodeinone-phenyltoloxamine-resin complex.

†Histionex, brand of phenyltoloxamine resin-complex.

bination would indeed be fully active as a clinically potent cough suppressant for a relatively long period of time and utilizing an exceedingly small dose of the drug.

IN HUMANS. While many antitussive preparations contain dihydrocodeinone as the bitartrate, none of these are active for more than a few hours when given in a 5 mg. dose. It is always desirable to use the minimum amount of medication which is effective in treating the conditions requiring the medication, therefore, clinical studies were undertaken using a preparation containing 5 mg. (approximately 1/12 grain) of dihydrocodeinone and 10 mg. of phenyltoloxamine as their resin complexes. Table 2 records some of the results obtained.

It will also be noted from the data in Table 2 that the 5 mg. (approximately 1/12 gr.) dose effectively suppresses coughs resulting from a variety of causes for an unexpectedly long period of time. A double dose (equivalent to 10 mg. of dihydrocodeinone) appears to have a somewhat longer effect. In order to compare the antitussive effect of the resin-complex product with standard therapy, those cases presented in Table 1 having coughs which persisted for a period of more than several days were first placed on either a preparation containing codeine desoxyephedrine and

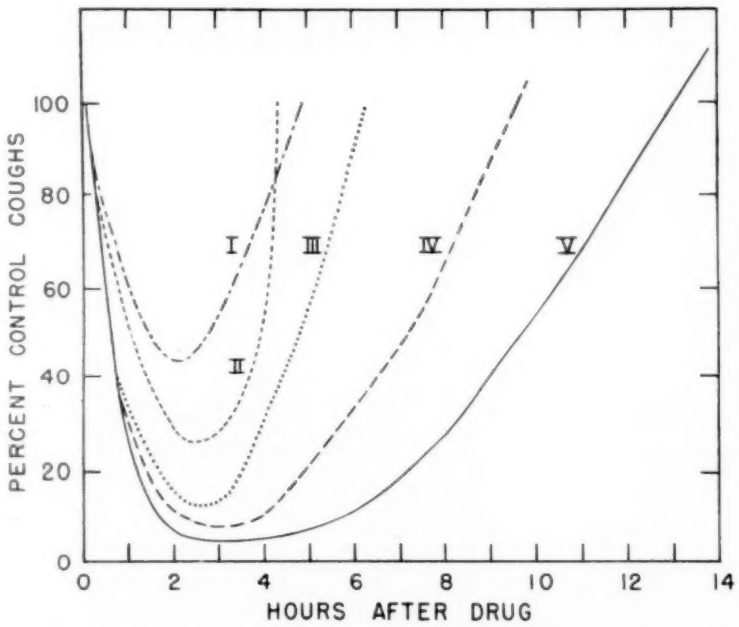

Fig. 1.—Suppression of coughs in dogs with orally administered codeine derivatives.

Curve I Response of 4 dogs to 2.2 mg. of codeine as the phosphate per kg.
Curve II Response of 8 dogs to 2.2 mg. dihydrocodeine as the bitartrate per kg.
Curve III Response of 5 dogs to .37 mg. of dihydrocodeinone as the bitartrate per kg.
Curve IV Response of 4 dogs to .37 mg. of dihydrocodeinone as the resin-complex per kg.
Curve V Response of 5 dogs to .37 mg. of dihydrocodeinone and 2.2 mg. of phenyltoloxamine as their resin-complexes per kg.

TABLE 2.—ANTITUSSIVE EFFECT OF DIHYDROCODEINONE-PHENYLTOLOXAMINE-RESIN-COMPLEX

Diagnosis	*Duration of Cough Prior to Treatment*	*Degree or Frequency of Untreated Cough*	*Length of Administration Days*	*Results*	
				Degree	*Duration in Hours*
		ONE DOSE EVERY 12 HOURS			
Acute respiratory infection	3 weeks	Intermittent	1	Excellent	8 to 9
" " "	4 "	Often	3	Fair	6 to 8
" " "	1 "	Occasional	2	Excellent	12
" " "	1 "	Frequent	1	Good	8 to 9
" " "	2 "	Occasional	2	Good	6 to 8
" " "	2 days	Frequent	5	Excellent	10 to 12
" " "	2 "	1 to 2 spells per hour	3	Excellent	12
" " "	2 "	2 to 6 " " "	3	Excellent	10 to 12
" " "	1 "	1 to 4 " " "	4	Excellent	10 to 12
" " "	3 "	2 to 3 " " "	3	Good	6 to 8
" " "	2 "	1 to 4 " " "	3	Excellent	8 to 10
" " "	2 "	3 to 4 " " "	3	"	8 to 10
" " "	1 "	3 to 6 " " "	2	"	12
" " "	3 "	1 to 2 " " "	4	"	8 to 10
" " "	1 "	1 to 4 " " "	2	Good	10
" " "	4 "	Morning and night	4	Excellent	12
Bronchitis	3 "	Occasional	1	"	10 to 12
"	2 months	4 to 6 spells per hour	4	"	10

Chronic sinusitis	5 to 6 years	1 to 2 " " "	7	Good	10
" "	2 to 3 months	Occasional	4	"	12
" "	2 to 3 weeks	2 to 3 spells per hour	7	Excellent	8
" "	2 "	1 to 2 " " "	7	"	8 to 10
" "	1 to 2 years	Morning and night	7	"	10 to 12
" "	Several years	" " "	7	Good	8 to 10
" "	6 to 8 "	" " "	7	"	6 to 8
" "	2 weeks	1 to 2 spells per hour	7	Excellent	8 to 10
Pharyngitis—slight	2 days	Occasional	1	"	12+
Irritation to smell of smoke	Whenever in contact		1	Fair	6 to 8
Pulmonary TB	3 to 4 months	Often (day and night)	41	Excellent	10 to 12
" "	6 to 8 "	" " " "	3	Good	6 to 8
" "	2 "	" " " "	8	"	6
" "	10 days	Occasional	12	"	6 to 7
Pulmonary TB with cold	3 weeks	30 or more spells daily	5	Excellent	6 to 8
" " " "	6 to 8 months	"All the time"	14	"	10 to 12
"Cigarette hack " "	Several years	Episodic—especially in morning	14	"	10
" "	2 weeks	Episodic—especially in morning	6	"	10 to 12
DOUBLE DOSES EVERY 12 HOURS					
Pulmonary TB with cold	3 weeks	Day and night hacking	5	Excellent	10 to 12
" " " "	6 to 8 months	Very often day and night	7	"	10 to 12
" " " "	2 "	Very often day and night	2	"	10+*

* There were no side effects in any of the above cases with the exception of this one patient when vomiting occurred 24 hours after the administration of the two-tablet dose. He has since been shown to be very sensitive to drugs in general.

prophenpyridamine or elixir terpin hydrate, both plain or with codeine given every 4 hours. The patients themselves consistently were of the opinion that much better and longer relief was obtained on the single dose of the resin-complex than was given by the other preparations at frequent intervals. This was confirmed in hospitalized patients who, although previous medication had failed, found the single dose of resin-complex permitted them to sleep through the entire night.

Discussion. During the course of the study, it became obvious that the drug was fully effective in suppressing coughs, and, in addition, the patients themselves commented on the rapidity of suppression of the cough and made statements to the effect that it was now possible to sleep all night, and that they were freed during the daytime from the necessity of taking repeated doses. Furthermore, it was noticed clinically that while the dihydrocodeinone-phenyltoloxamine-resin-complex effectively suppressed the useless or hacking cough, the less frequent productive cough still appeared and performed its physiological role.

In addition to the superior effect of resin-complex product, single dosage form medication was not only more convenient than the usual q.i.d. dosage, but the therapeutic benefits seemed to be much smoother and more uniform.

Summary. The predictably sustained response of patients to a dihydrocodeinone-resin-complex in presence of a phenyltoloxamine-resin-complex meets the need for an antitussive preparation which predictably suppresses for an 8- to 12-hour period the hacking, nonproductive cough, yet does not completely abolish the natural protection of the cough mechanisms.

Suppression of the useless cough for 8 to 12 hours after administration of one dose of this material (equivalent to 5 mg. of dihydrocodeinone) was superior to results usually obtained with the same amount of the drug taken every 2 to 4 hours.

No side reactions were observed. This is consistent with the low dosage necessary when a potentiated resin-complex is used.

It would appear that the dihydrocodeinone-phenyltoloxamine-resin-complex fills a need for a product which releases the drug on a predictable basis for a period of time which permits administration once every 12 hours.

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(Interlingua on page 226)

PROGRESS
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SURGERY

UNDER THE CHARGE OF

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AN EVALUATION OF THE MECHANISM AND TREATMENT OF COMPLETE RECTAL PROLAPSE

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PROLAPSE of the rectum has attracted the attention of surgeons for centuries but little or no progress in the understanding of this condition, nor in its treatment, was made until the past 50 years. It is well, therefore, to re-examine the subject of rectal prolapse involving the entire rectal wall in the light of our present knowledge. The medical literature reveals that this condition is characterized by varied concepts which deal with nearly all phases of the problem. An explanation for the variability in these opinions is found in the different possibilities one might encounter when he identifies the nature and extent of the prolapsing part along with the circumstances under which the prolapse occurred. This has led to differences in descriptive terminology and classifications. General observations as to predisposing causes and the types of individuals most commonly affected have been made and variously interpreted. At times, it has been thought that the causative factor is a defect in the anatomy or physiology of the prolapsing part, with a secondary deformation of the opening in the pelvic floor. An opposing view is that there is predominantly a primary defect in the support offered by the pelvic floor accompanied by the development of a peritoneal sac such as

occurs in a hernia. The early operative procedures were directed at the prolapsing part as it presented externally and later operations included intra-abdominal revisions of the reduced bowel and its supports. The principles of hernia repair have been applied in methods which also differ according to the concepts held. Many of the proposed operations have not involved the pelvic floor whatsoever, and it seems noteworthy that there have been few, if any, operations in which the component parts of the pelvic floor were considered and revised in order to restore the normal angle between the rectum and anal canal. This mechanism provides a natural protection for the rectum when it is subjected to its greatest stress. The major operative procedures performed today result in an acknowledged recurrence rate and a concession that the ultimate surgical techniques are being steadily approached but possibly are not yet at hand. After reviewing these concepts, we will emphasize the natural protection afforded to the rectum by the pelvic floor. Attention to the reconstruction of this factor which is both anatomical and physiological may well further the advance toward a more permanent surgical cure.

Definition. The application of identifying terms to a descensus of a portion or all layers of the intestine through the anus is by usage descriptive only of the displaced structure. This is in contrast to bowel herniations from other abdominal cavity orifices wherein the anatomical site of the opening is given and the protrusion is called a hernia. Since obviously the floor of the abdominal cavity is affected, the displaced portion of the bowel must descend or fall downward which accounts for the use of the term prolapse. The designation of mucosal involvement alone as an incomplete prolapse and protrusion of all layers of the wall of the rectum as a complete prolapse occurs in the earliest discussions (Cripps[12]) of the subject as well as at present. More recently the term procidentia has been used to mean the same as a complete prolapse, but acceptance of this term has not been universal, despite the fact that it has been used for over a hundred years[27].

Classification. The classifications which have been proposed are different because some of them have attempted to explain the mechanism of prolapse whereas others have been limited to the objective anatomical findings. Thus, Martin (1932)[37] used a classification which followed the manner in which he thought a prolapse developed. He regarded the onset as an intussusception of the rectum or recto-sigmoid bowel, as an internal or concealed entity. This, he called a first degree prolapse. After the prolapse descends to become externally visible, he considered it a second degree prolapse. At this stage, the lowermost portion of the rectum is not displaced and a sulcus is found between the retained rectum and intussuscepted bowel. If descent continues, the entire rectum must reverse itself and become continuous with the skin margin at the anal canal. Martin termed this a third degree prolapse.

In contrast to this classification, Tuttle (1896)[65] used the same terms, but applied them according to the severity of the prolapse without regard to the mode of development. Thus, a simple 2-tube eversion without a sulcus is a first degree prolapse. The presence of a sulcus with an external protrusion is a second degree prolapse, whereas a concealed or internal intussusception is a third degree prolapse. In other words, Tuttle's first degree prolapse is the same as Martin's third degree prolapse.

Another classification is that of Bacon[4] which disregards the sequence in development or severity of the prolapse, but accounts for all the anatomical possibilities. This is accomplished by defining three variables: first, the anatomical site; whether it be anal canal, rectum, or sigmoid colon. Secondly, a provision is made as to whether the involvement is external or internal. Finally, involvement of the mucosa alone is termed a prolapse, whereas involvement of all layers of the bowel is a procidentia.

Since the problem is largely that of external protrusion, a classification will have the greatest simplicity if it is limited to the anatomical identification of such a situation. Accordingly, a widely used concept depends only upon examining the protruding part and determining whether it is mucosa alone or consists of all layers of the rectum. A mucosal eversion is termed an incomplete prolapse and a decensus of all layers is a complete prolapse. As previously mentioned, the term procidentia is used synonymously with complete prolapse. The two terms, incomplete prolapse and complete prolapse, will identify the great majority of the problems which are presented. In addition, there is one other condition which presents a somewhat different situation and is infrequent. This is a sigmoidorectal intussusception which initially is concealed, but continued progression will cause it to become external. It is identified by the deep sulcus around the prolapse indicating that a large portion of the rectum is not everted.

It is not intended to discuss the simple mucosal prolapse since the treatment in general is satisfactory. Likewise, the prolapse of a sigmoidorectal intussusception will not be considered because the problem does not involve the pelvic floor.

Complete Rectal Prolapse. INCIDENCE. The occurrence of complete rectal prolapse is not common, and accurate figures concerning the incidence are not available. An idea of its frequency is suggested by reports of the various series published by outstanding clinics and by surgeons especially interested in the condition. Miles (1933)[41] reported a series of 31 cases. Hayden (1947)[25] reported 60 cases. Swinton (1955)[61] reported the experience of the Lahey Clinic of 52 cases covering a 15-year period. Pemberton (1953)[50] reported a series of 173 patients treated at the Mayo Clinic. Finally, the St. Marks Hospital (London) Staff (1949)[70] reported a group of 231 patients observed over a 17-year period.

Complete rectal prolapse is more common in women than in men, and there is a definite tendency for it to occur at the extremes of age. A general impression exists that it is common among institutionalized mental patients. The largest group of patients reported in the literature is the St. Marks Hospital group referred to above. Of 231 patients with complete rectal prolapse, 16 were children. Female patients with prolapse were 6 times more frequent than male patients. In females, the maximum incidence occurred in the later decades of life, while in males the highest incidence was in the second and third decades. The number of mental patients in this group was not impressive, there being only 10 such patients.

ETIOLOGY AND MECHANISM. It is probably improper to state that the etiology or mechanism of complete rectal prolapse is unknown. Many of the factors involved are recognized and the difficulty is in awarding the proper degree of importance to each factor, a problem that may be different from patient to patient.

The erect posture has placed demands upon the pelvic floor far in excess of those placed upon the pelvic musculature in quadrupeds. In man, the pelvic muscles in combination with the bony pelvis must contribute to the support of the pelvic viscera and at times oppose the forces which are provided to evacuate the content of these viscera, thereby providing continence. The emptying of the viscera through tubes which pass through the pelvic diaphragm requires a precise balance of factors which will result in unopposed evacuation of the content and yet not permit the visceral tube itself to be expelled outwardly from the pelvic cavity. From the quadruped state, such a mechanism has been arrived at by a process of evolution and it might well be more efficient were it not for the requirements of pregnancy and partuition.

From these remarks it follows that as regards the rectum, there is an interplay of forces upon the pelvic floor. One is an expulsive or thrust factor which includes the various mechanisms by which the intra-abdominal pressure is elevated and also includes the muscular propulsive waves, the summation of which results in evacuation of the colon content. In opposition to this expulsive factor are the retaining factors. Some of these prevent incontinence of the bowel content and others prevent expulsion of the rectum itself. A balance develops between the expulsive factors and the retaining factors which is very broad in that there is a wide margin of safety. Accordingly, even though the retaining factors may be somewhat deficient, and the expulsive factor greater than usual, prolapse need not be expected to occur. Excessive and prolonged application of the expulsive factor, on the other hand, will promote the development of prolapse even in the presence of normally developed retaining factors.

Another possibility permitting prolapse is a weaker than normal expulsive factor being opposed by a yet greater inadequacy of the retaining factors. It is to be emphasized that in all conceivable combinations of expulsive forces versus retaining forces, the actual occurrence of prolapse is often dependent upon just the right combination of these opposing factors. This explains the infrequency of complete rectal prolapse.

EXPULSIVE FACTORS. The nature of the expulsive factor is twofold, one relating to the application of an increase in intra-abdominal pressure to the rectum, and the other inherent in the forward peristaltic waves of contraction in the bowel wall. The discussion of these factors is found in the usual description of voluntary defecation. Initiation of this act is accomplished by increasing intra-abdominal pressure. Compression of the abdominal cavity is most effectively done by a sustained depression of the diaphragm, and to a lesser degree by flexing the spine and flexion of the thighs upon the abdomen. If previous colon peristalsis has recently brought a fecal mass from the sigmoid reservoir into the rectum, the resultant pressures are applied to a distended rectum. The rectal distention elicits involuntary reflexes which cause proximal colonic peristalsis with a propulsive pattern. After these reflexes have come into play, the actual emptying of the rectum and colon is assisted by application of further increases in abdominal pressure. It follows that sudden increases in intra-abdominal pressure for other reasons, such as encountered in crying, retching, coughing, weight lifting, or forcible micturition, will tend to expel the rectal content and also to push the rectum through the pelvic floor. Similarly, an increase

in colon peristalsis, such as encountered in prolonged diarrhea, will likewise tend to carry the rectum externally.

RETAINING FACTORS. The retaining factors were classified by Maes (1926)[35] into 3 groups: The first consists of the mechanical suspension of the rectum and lower colon and is called passive support. The second is related to the geometric manner in which the rectum descends from the peritoneal reflection to the sphincteric level. This is termed conformation and position and permits dissipation of pressures applied from above to the rectum into many different directions. The third factor refers to the resistance offered by the pelvic floor and is termed active support. We have given this factor 2 subdivisions, the first being related to the protection offered by a muscular ring in the abdominal cavity to herniation of a peritonal sac[48]. The second subdivision refers to the function of the levator muscle which is both supportive to the rectum and by contraction is capable of angulating the rectum relative to the anal canal.

PASSIVE SUPPORT. The passive support includes the peritoneal folds, the mesentery of the left colon, especially that of the sigmoid and rectum, and the various fibrous attachments to the sacrum, vagina and prostate gland. Much importance has been placed upon the lateral attachments often called lateral ligaments, which suspend the rectum to the lateral walls of the pelvis. These supports are demonstrable during operative procedures in which relaxation is obtained by spinal anesthesia. Under such circumstances, a point on the rectal wall about 8 cm. above the anorectal line can be brought down by traction to approach the level of the anal canal. The amount of traction necessary is appreciable and is a measure of resistance of the rectum to eversion.

Lynch (1927)[34] stated that the quality of connective tissue varies in individuals and that the structural tone of the body is dependent upon the quality of the binding connective tissue. Weaknesses in these structures may be a reflection of nutritional deficiencies and general debility. Connective tissue, if subjected to long continued stress, is known to stretch and it is unlikely that fibrous tissue alone can withstand continued pressure or traction without stretching. This accounts for the voluntary development of rectal prolapse reported in a certain religious cult[70].

In anomalous situations in which there is a mesentery of the rectum down to the anus, the incidence of prolapse is increased. A long redundant sigmoid bowel, especially if the descending colon is not firmly fixed, also increases the tendency to rectal prolapse.

CONFORMATION AND POSITION. Conformation and position refers to the concept that the rectal curvatures have an important stabilizing influence. The rectum normally develops rather marked anteroposterior and lateral curves which help to fix it in position. The net effect of these curvatures is to disperse the expulsive or displacement forces coming from above, and thus prevent their full application in a direct line to the opening in the pelvic floor.

The vertebral curvatures are not fully developed in infants and young children. The sacrum is relatively straight and the pelvic tilt has not yet occurred. Consequently, the rectum is more or less straight and the expulsive factors from above act more directly upon the pelvic floor. This results in an abnormal degree of stress which accounts for the higher incidence of prolapse in infants. Normally, as the child develops, the lumbar and sacral curves become prominent and the pelvis tilts forward. These changes tend

to counteract the force of gravity on the pelvic diaphragm. The marked forward curvature of the lumbar spine places a firm shelf under the abdominal viscera and deflects their weight to the muscles of the abdominal wall, and onto the pubic bone[42,66]. An arrest in the development of the vertebral curvatures and the pelvic tilt contribute to an increased work load upon the pelvic floor, and thereby increases the tendency to prolapse.

ACTIVE SUPPORT: HERNIA PROTECTION. The concept that a rectal prolapse is a sliding hernia involves a consideration of a hernial ring and the development of the peritoneal sac. The hernial ring is the circular muscular protection provided at abdominal cavity orifices which must permit entry or exit of tubular structures. This ring is subject to stresses set up by increases in intra-abdominal pressure, the pressure being applied against all peritoneal surfaces, parietal and visceral. A displacement of any particular portion of the peritoneum depends upon the weakness of the supporting tissue immediately beneath it. In the case of the pelvic floor, the peritoneal reflection which crosses from the mid-sacral level anteriorly to either the uterus or male bladder, is usually suspended at about 10 to 18 cm. above the anal outlet. The intervening tissue provides inherent protection from herniation of a peritoneal sac. It follows that as the cul-de-sac is lower and approaches the level of the floor, the protection is less. To carry such an idea further follows the concept outlined by Moschowitz in 1912[43], and now widely accepted. He described the weak point in the support of the peritoneum in a low cul-de-sac as being in the anterior rectal wall. Increases in intra-abdominal pressures will then force a progressive invagination of this anterior rectal wall which may ultimately be forced through the sphincter opening. Examination of such a prolapse will reveal a predominance of anterior rectal wall in respect to the posterior wall so that the lumen of the prolapsed segment appears to be displaced posteriorly. The peritoneal lining of the resultant sac will be partly visceral and partly parietal, the visceral portion constituting the serosal surface of the prolapsed anterior rectal wall. Such a situation is a sliding hernia. As in all hernias, the management of the peritoneal sac precedes the revision of the muscular support offered by the externally applied supportive ring. If one accepts this hernia as a sliding hernia, then the treatment of the usual hernial sac, that is excision and high ligation, is impossible. Rather, the sac must be turned inside out which is accomplished by inversion, a maneuver which occurs when the rectum is restored to its normal position. The possibility of a complete rectal prolapse being a type of sliding hernia potentially opens a space for inclusion of a loop of small bowel between the peritoneal surfaces included in the anterior wall of the prolapse. This might occur on occasion and is mentioned in nearly all the early literature. Its occurrence, however, is questionable since these serosal surfaces are well opposed to each other and the depth of the resultant sac is probably no greater than 5 or 10 cm. when measured from within.

The Moschowitz explanation regards the low cul-de-sac as a causative factor in the development of rectal prolapse. However, it is also possible that the descent of the peritoneum occurs as the result of traction, in that the prolapsing rectum pulls the pelvic peritoneal reflection down with it. Restoration of the descended bowel followed by adequate fixation in the pelvic cavity will cause inversion of the peritoneal sac. The application of increased abdominal pressures to an inverted sac will be of

no consequence as far as contributing to recurrence of the hernia.

ACTIVE SUPPORT: LEVATOR ANI FUNCTION. The role of the levator ani muscle as a retaining factor is a dynamic mechanism, the variations of which are provided by contraction and relaxation of the muscle. In the quadruped animal, this muscle is represented by a group of muscles whose main function is to activate the tail[19,63]. With the assumption of the erect posture and with the loss of the tail structure, these muscles in man have changed their function. They have not atrophied; rather they have fused and adapted themselves primarily to support the pelvic viscera. This support problem is complicated by the fact that three structures: the rectum, vagina, and urethra, pass through the pelvic floor.

What is the mechanism by which support and function is accomplished? It has been known for years that the levator ani muscle, as the name indicates, elevates and supports the distal end of the rectum. This function has been demonstrated recently by Roentgen myography[8]. The levator muscle is injected with a radiopaque substance and roentgenograms are taken with the patients contracting and relaxing the sphincteric musculature. Lateral films with barium in the rectum will demonstrate the same function[48]. These studies show that in the erect position, the rectum passes forward almost horizontally upon the levator muscle and terminates in an acute angle with the anal canal which is directed posteriorly and downward. On contracting the levator and sphincter muscles, the distal end of the rectum is pulled upward and forward even more. This results in increased angulation, which in turn increases the fixation and protection. With relaxation of the levator, and increased intra-abdominal pressure, the rectum assumes a more or less vertical position. The angle is largely obliterated and the rectum is directly above both the hiatus in the pelvic diaphragm and the anal opening. The rectum empties in this position. In patients with prolapse, the myography studies of Berglas and Rubin[8] found this levator mechanism deficient. The rectum remained in the vertical position constantly and there was a loss of the anorectal angle.

It appears that angulation is an important general anatomical mechanism for achieving continence. For example, the esophagus penetrates the diaphragm to join the stomach at an acute angle. Allison[1], in his studies of esophago-gastric continence, feels that the acute angle which is formed at the junction of the esophagus and stomach is the means by which reflux is prevented. Similarly, the bladder neck joins the urethra at an acute angle and is supported by the levator muscle[45]. Urologists have had success in treating stress incontinence by re-establishing this acute angle by means of a fascial sling placed around the urethra and attached to the symphysis pubis[52,58].

Various ductal structures enter hollow organs in an oblique manner in order to effect closure during periods of increased tension in the hollow organs. Examples of this are the common bile duct entering the duodenum; the fallopian tube entering the uterus and the ureter entering the bladder. During periods of distention of the receptacle organ the entering duct structure is rendered continent by an exaggeration of the oblique entrance of the conduit. These examples indicate the protective influence of angulation in effecting continence. The lower rectum appears to utilize this principle by the establishment of an acute angle at the level of the pelvic floor. This

angle is present normally; is increased during periods of stress, and is obliterated only during evacuation of the rectum. This mechanism results, as described previously, from the action of the puborectalis portion of the levator ani muscle.

Treatment. HISTORICAL. The early treatment of complete rectal prolapse consisted of amputation of the external bowel, described by Hey[27] in 1805, and again by Auffret[3] in 1882. A similar procedure was done over a bougie by Esmarch (1888)[20] and in a more stepwise formal manner by Mikulicz[40], Billroth[10], Nicoladoni[47], and Treves[64] (1888–1890). In these procedures no apparent consideration was given to the mechanism or possible cause of the prolapse insofar as attempting to modify the pelvic floor. Revision of the lower rectum was suggested by Roberts in 1890[56]. This operation narrowed the rectum like a funnel by resecting an inverted triangular wedge from the posterior wall. This is similar but more extensive than the operation described by Gross (1872)[24]. The base consisted of a section of the sphincter, the edges of which were resutured. This narrowing of the lower rectal segment and stricturing of the sphincteric ring was intended to support the prolapsing bowel from below.

Support of the prolapsing bowel from above was first recommended by Allingham in 1888, and done by Brigade Surgeon McLeon in 1891[39], on a 19-year-old boy in Calcutta, India. The atony of the pelvic floor permitted the operator to insert his forearm into the rectum so that he could press the sigmoid colon against the anterior abdominal wall and secure it by blind suture. This was supplemented by an abdominal wall incision and suturing of the previously secured bowel to the wound. Soon thereafter, many abdominal operations were directed toward supporting the rectum and sigmoid colon from above. Berg (1892)[7], sutured the mesorectum to the posterior parietal peritoneum. Fixation of the sigmoid colon to the anterior abdominal wall by a temporary left iliac colostomy was introduced by Jaennel in 1889[30], the colostomy requiring 4 attempts at closure before succeeding. Noteworthy is a report by Bryant[11] of a diversionary colostomy done for prolapse in 1893. The colostomy was not supportive and the patient was not seen for 6 months, during which interval there was complete return of sphincter tone and the prolapse could not be produced by severe straining. Bryant concluded that defecation contributes to advancement of the disease. Suture of the sigmoid colon to the anterior abdominal wall was reported in 29 cases by 1897[11]. Resection of a segment of the sigmoid colon before its ventral fixation was done by von Eiselsberg in 1902[17].

During the next two decades, attempts to augment the fixation and support of the rectum were applied from both above and below the pelvic floor. It is questionable to what degree the operator was influenced by what he thought was the mechanism of prolapse as to what procedure was chosen. It is more probable that the patient's general condition and the willingness of the surgeon to risk a laparotomy decided wherein the surgery was directed. A comprehensive review of all operative procedures in the early surgery of rectal prolapse appeared in 1912 by Moschowitz[43], at which time he also introduced his hernia concept. Moschowitz groups the operations into 4 large categories. The first are designed to narrow the anus and include the mucosal resection and submucosal reefing operation of Bier[9] along with the elliptical resection of rectal mucosa by Delorme[14] and the wedge resec-

tions performed by Diffenbach[15] and by Roberts[56]. Also noted, is the circumferential insertion of a silver wire in 1890 by Thiersch[62]. This effectively stenoses the outlet and still finds application in the treatment of reducible rectal prolapse in the poor risk elderly patient.

The second group includes those operations which strengthen the natural supports of the rectum by repairing the pelvic floor from below. The approach is either behind the anus (Hofmann, 1905[29]) or anteriorly (Napalkow[46]). Support is obtained by approximation of the levator muscles and in the operation of Beresnegowsky[6], the repair is supplemented by portions of the glutei muscles.

The third group includes methods intended to fix the rectum and is divided first into those operations done through a coccygeal approach. Included are the operations of Verneuil[67], Marchant[36], and Ekehorn[18] resulting in securing of the rectum to the sacrum or posterior integument. Sick[59] inserted a tamponade in the retrorectal space. The second division for operations in this group includes those fixation procedures applied from above by means of laparotomy. Jaennel[30], Weber[68] and Herzen[26] attached the sigmoid colon to the anterior abdominal wall, whereas Roller[57] attached it in a retroperitoneal pocket in the left iliac fossa. As mentioned earlier, von Eiselsberg[17] recommended a partial resection of the sigmoid colon before fixation of the remaining colon.

The fourth and final group accounts for those operations which resect the prolapse. These are the operations of Weinlechner[69], Esmarch[20], and Mikulicz[40].

The sliding hernia concept of Moschowitz called attention to an abnormally low cul-de-sac, leading to inversion of the anterior rectal wall, and the result was described by him as a "prolapse out of the rectum," rather than "prolapse of the rectum." The Moschowitz operation consisted of a series of concentric purse string sutures placed in the peritoneal floor from within, thereby obliterating the cul-de-sac. Subsequently, many operations have included the elevation of the cul-de-sac.

CURRENT TREATMENT. The evaluation of the treatment of complete rectal prolapse is facilitated by a classification of the various procedures as exemplified by the above-mentioned classification of Moschowitz. Other classifications have tended to follow this broad outline and in general, the objectives of surgery have been: (1) constriction of the anus; (2) fixation of the rectum; (3) resection of the prolapsing bowel; (4) obliteration of the peritoneal sac; (5) repair of the pelvic floor.

However, since we have classified the retaining factors which normally protect the rectum in the discussion of the mechanism of prolapse, we prefer to follow this same classification and group the operations according to the type of rectal support each procedure attempts to restore:

1. Operations which restore passive rectal supports.
2. Operations which restore rectal contour (conformation and position).
3. Operations which restore active rectal supports.

OPERATIONS WHICH RESTORE PASSIVE RECTAL SUPPORTS. This includes the injection of mildly irritating chemicals into the submucosa of the rectum and into the peri-rectal tissues producing an inflammatory reaction resulting in fibrosis, which in turn assists in passively supporting the rectum. Various chemicals have been used, 5% phenol and oil and 5% quinine and urea hydrochloride being the most popular.

This form of treatment has not been effective in complete prolapse in adults. It is sometimes used for children. It is generally accepted that it is more effective in incomplete prolapse than the complete type.

The destruction of portions of the rectal mucosa by chemicals or by electrocautery applied to its surface has been used but is not effective where all layers of the bowel are involved.

Years ago, Lockhart-Mummery[33] described a procedure which attempted to fix the posterior wall to the sacrum. This was done by opening the presacral space from below and packing it with gauze which he left in place for several days. It was felt that the reaction of the tissues would result in fibrous tissue formation between the rectum and sacrum and this would be sufficient to support the rectum. Unfortunately, this has not been successful according to a recent report from St. Marks Hospital[70] where this work originated.

A large number of procedures have been proposed which aim to fix the rectum in position from above. Mayo[38] reported success with an operation wherein the rectum is supported by a new peritoneal floor which in turn is supported by fascial strips at a high level. Frequent suggestions have been made for fixation of the sigmoid colon to the anterior abdominal wall, to the uterus, and to the psoas muscle tendon. Pemberton[50] advised freeing the rectum from its attachments, elevating it up taut and fixing it to the sacrum. He believes that following such a procedure, the rectum would remain fixed in its elevated position because of the formation of scar tissue in the retrorectal space. Orr[49] uses a similar method, fixing the rectum to the sacrum with fascial strips. Hirschman[28] suggested shortening the mesosigmoid by plication, thereby suspending the rectum.

The formation of a sigmoid colostomy is a type of suspension advocated by surgeons for many years. It is effective especially if all loose bowel is excised at the time the colostomy is made. However, we have seen one patient who developed a recurrence 3 years following closure of such a colostomy.

An indirect method of correcting loose passive supports is by excision of all redundant bowel. This has been the basis of much of the surgery of rectal prolapse. Miles first popularized the procedure by excising the bowel from the perineal approach. He first used it in 1904 and reported a series of 31 cases in 1933[41]. The method enjoyed wide acceptance in England and in this country until quite recently. Recurrences, however, are frequent and the method has been largely supplanted by abdominal resection. Nevertheless, it is a satisfactory palliative procedure in old, poor risk patients, especially if used in combination with Thiersch wire constriction of the anus. It is likewise a good operation in patients with strangulated prolapse of the rectum. M. R. Reid[53] advocated excising the prolapse by the application of an elastic ligature over a rigid tube, an operation previously performed by Kleberg[31].

Perineal excision of the prolapsed bowel has recently been revived by Dunphy[16] and by Altemeier[2], who, however, combine excision with repair of the pelvic floor. Possibly the most popular operation in good risk adult patients now is anterior resection. All excess bowel is excised and a primary end-to-end anastomosis is made. A new peritoneal floor is fashioned at a high level. Muir[44] feels that the reaction around the extraperitoneal suture line is in part responsible for its success.

since no attempt is made to repair the defect in the pelvic floor.

OPERATIONS WHICH RESTORE RECTAL CONTOUR (CONFORMATION AND POSITION). The only surgical procedure designed purely to re-establish rectal curvatures so far as we can determine is that advocated by Cromar[13]. He mobilizes the rectum as in an anterior resection, pulls it up out of the pelvis and arranges the bowel in folds by suturing loops together with non-absorbable sutures. He believes that by this maneuver, peristaltic rush is arrested at the level of the rectosigmoid and the rectum is converted into a more or less passive pouch with less tendency to prolapse. We have had no experience with this method of treatment.

OPERATIONS WHICH RESTORE ACTIVE RECTAL SUPPORT. One of the early methods of treatment of rectal prolapse was by restoration of the support provided by the anal sphincter muscle. Plication of the relaxed sphincter muscle has been a common method of doing this. However, in 1891, Thiersch[62] proposed constricting the anus with a silver wire loop placed in the subcutaneous tissues around the anus. This technique provides considerable support and may splint the area for a sufficient time to allow a return of function. The operation has recently been advocated by Gabriel[22] who first used it for incontinence, but who feels that it is effective in at least minor degrees of complete prolapse. It may have a place in the treatment of very old, poor risk patients. Other materials such as heavy silk, fascia and muscle have been used to surround and constrict the anus. Use of the gluteus muscle[60] has been advocated and recently Pickrell[51] has described a procedure using the long thin gracilis muscle to surround the anus. The muscle transplants were first suggested for incontinence but have also been accepted as substitutes for a defunctionalized sphincter muscle resulting from long continued stress.

Consideration of the treatment of the hernial sac is discussed with this group because it concerns itself with the pelvic floor. As previously mentioned, Moschowitz was convinced that rectal prolapse is a sliding hernia and advocated obliteration of the sac as the primary requisite for cure of rectal prolapse. Since the rectum constitutes one wall of the sac, he felt that obliteration by suture was the only safe method of dealing with the sac. He did not advise repair of the pelvic diaphragm and experience has shown that obliteration of the sac alone results in frequent recurrences. Ripstein[55] employed a fascial graft sutured to the anterior rectal wall and to the back of the uterus thereby supporting the cul-de-sac. This provides a firm anterior fascial support to prevent formation of a sliding hernial sac. Consequently, while the sliding hernia concept is widely accepted, most surgeons advise other procedures in addition to treatment of the sac.

Operative procedures emphasizing the repair of the pelvic diaphragm which in essence means repair of the levator ani muscle have been suggested for years. Many early surgeons felt that prolapse is a condition of incompetence of the levator ani muscle, especially the puborectalis portion of it. Lange (1887)[32] suggested suturing the levator muscle together posterior to the rectum after excising the coccyx. Barrett (1909)[5] made a strong plea for the repair of the pelvic floor. He felt that the defect in the pelvic diaphragm is the important factor, not the sac; that the rectum is normally firmly attached to the levator muscle, but that in prolapse it becomes detached. For correction of rectal prolapse, he advised excision of the prolapse from

below and in addition, suture of the levator ani muscle both anterior and posterior to the rectum, being careful to suture the muscle to the bowel. In 1925, Maes and Rives[35] recognized the importance of reconstructing the pelvic floor and advised a similar operation. Graham (1942)[23] advised suturing the levator muscles together anteriorly from above. This method is difficult technically and has not been generally accepted. Dunphy[16] and Altemeier[2] have urged perineal operations which include excision of redundant bowel, elevation of the peritoneal sac and reconstructing the pelvic floor by suturing the levator muscles together in front of the rectum. In 1920, Richter[54] advocated restoring rectal support posterior to the rectum. He did this by passing a portion of the broad ligament in back of the rectum so as to make a suspensory hammock for the lower rectum.

RESTORATION OF THE ANGLE BETWEEN RECTUM AND ANAL CANAL. One of us[48], impressed with the support provided the rectum by the levator muscle, studied the lifting mechanism of the rectum which results from the contraction and relaxation of the levator muscle. Clinically, it seemed apparent that this lifting mechanism is deficient in patients with severe degrees of rectal prolapse. A similar situation exists with respect to the bladder and urologists have devised an operation to correct the lifting mechanism by placing a fascial sling around the bladder neck and attaching it to the pubis.

We felt that an effective degree of support to the rectum would be possible by supporting it in a similar manner by a fascial sling. A piece of fascia lata about 3 by 25 cm. is placed transversely across the lower rectum just above the sphincter muscle. The approach is transcoccygeal and the rectum is freed posteriorly and as far forward as possible. The graft is firmly fixed to the rectum with non-absorbable sutures and the ends of the graft are pushed forward around the rectum as far as possible. A retropubic extraperitoneal incision is made and the ends of the graft are sutured to the posterior surface of the pubis. Finally, a silver wire is placed in the subcutaneous tissue around the anus (Thiersch procedure) to support the sphincter and to hasten return of function. No attempt is made in this operation to obliterate the peritoneal sac. As indicated above, we believe that if the rectum is supported in its normal position, the sac becomes inverted. We have had success with this type of support in 5 patients, one for over 5 years. We believe that the sling provides an effective support for the rectal ampulla; fixes it at the level of the pelvic floor and angulates the distal rectum with respect to the anal canal, all of which restore rectal fixation and prevent prolapse. We have roentgenologic evidence which indicates that after a time the lifting mechanism is re-established to a fair degree by this procedure[48]. This cannot be due to the inelastic fascial insert, but rather, we believe it is due to a partial return of strength and function of the levator muscle, resulting from the artificial support.

Complete rectal prolapse has been a perplexing problem as evidenced by the large number of different operations which have been used in this condition. These have been designed either to constrict the anus; fix the rectum; resect the prolapsing bowel; obliterate the peritoneal sac or to repair the pelvic floor. The application of any one of these methods alone has been inadequate, which has resulted in the use of a combination of these procedures[21]. These operations have, in general, been based upon ana-

tomical considerations for the most part. In addition to these morphological concepts, it has long been our feeling that a restoration of physiological function is likewise a goal to be attained. The changes in position of the rectum with respect to the anal canal in the normal individual during defecation provides a mechanism of support in normal patients and it is quite likely that without this directional change of the rectum during stress, all individuals might be subject to rectal prolapse. It is therefore our belief that progress in the treatment of rectal prolapse will be made through a consideration of the physiological factors involved as well as the anatomical factors.

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SUMMARIO IN INTERLINGUA

(See page 207 for original article)

Un Complexo a Resina Como Agente Antitussive a Efficacia Prolongate

Le predicibile duration del responsa del patientes a un complexo de dihydrocodeinona e resina in le presentia de un complexo de phenyltoloxamino e resina satisface le desiderato de un agente antitussive que supprime predicibilemente pro un periodo de 8 a 12 horas le stridulente tusse non-productive sin supprimer completemente le protection natural del mechanismo tussiente.

Le suppression del inutile tusse pro 8 a 12 horas post le administration de un dose de iste material (equivalente de 5 mg de dihydrocodeinona) esseva superior al resultatos usualmente obtenite per administrationes del mesme quantitate del droga omne 2 a 4 horas.

Nulle reactiones lateral esseva observate. Isto corresponde al basse dosage requirite quando un complexo a resina potentiate es usate.

Il pare que le complexo de dihydrocodeinona e phenyltoloxamino con resina satisface le desiderato de un producto que libera le droga predicibilemente in le curso de un periodo de tempore de maniera que il deveni possibile administrar lo solmente un vice omne 12 horas.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.

AND

HENRY P. WAGENER, M.D.

THE INFLUENCE OF DRUGS ON THE CHOROIDAL CIRCULATION OF EXPERIMENTAL ANIMALS

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THE choroid forms the middle layer of the eye and is bounded externally by the sclera and internally by the retina. The choroid is a highly vascular tissue containing four-fifths of the circulatory apparatus of the eye[17] and contributing greatly to the nutrition of the retina. Because of its inaccessibility for studies *in vivo*, this tissue has not been extensively investigated until recently.

Many ocular diseases may be attributed directly or indirectly to lesions in the choroid, the vascular coat of the eye. The role of the choroidal circulation in the causation, and in the possibility of control, of a number of pathologic ocular processes, such as glaucoma and senile macular degeneration, remains to be clarified. Partial solution of some of these problems may some day be obtained by discovery of the various influences of certain therapeutic agents on the choroidal circulation. Ashton stated, in 1952[3], "that after more than two centuries of careful research it is remarkable that our information upon some of the essential points should remain so inadequate." However, in recent years some improvements have been made, at least in methods for studies *in vivo* of the choroidal vasculature in experimental animals. Review of the salient findings obtained by these improved methods of study seems justified at this time.

ANATOMY OF THE CHOROIDAL VASCULATURE. In man, the vascular layers of the choroid have been divided into three superimposed strata. The largest vessels traverse the layer nearest the sclera, beneath which lie the vessels of medium size, while innermost lies the capillary layer, or choriocapillaris. The choriocapillaris is essentially a delicate, capillary membrane composed of numerous closely packed capillaries, which take on larger caliber and have wider interstices near the periphery, or ora serrata. As a rule, the more active

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the function of the organ, the closer is its capillary network and the larger is its blood supply. It is interesting that the choriocapillaris and the pulmonary capillaries comprise the finest and most densely packed capillary beds in the body[23].

By introduction of neoprene latex into the choroidal plexus, Ashton[3], and later Wybar[49,50], made great contributions in elucidating the finer anatomy of the choroid. Ashton[3] has shown that the bulbous swellings of the veins are not arteriovenous anastomoses as previously was believed, but that they are produced by arterial compression of the veins. The existence of arteriovenous communications in the choroidal vascular tree also has been denied by subsequent authors[21,47].

In man, the choroid is supplied posteriorly by 10 to 20 short ciliary arteries that pierce the sclera about the optic nerve and two long posterior ciliary arteries that course along the horizontal meridian on each side of the globe to pierce the sclera and enter the choroid. These ciliary arteries arise from the ophthalmic branch of the internal carotid artery. The anterior portion of the choroid is supplied by the recurrent ciliary arteries, which arise from the major circle of the iris formed by the anterior ciliary arteries as well as by the long posterior ciliary arteries. The anterior ciliary arteries arise from the arteries that supply the rectus muscles, which in turn arise from the ophthalmic artery. These recurrent ciliary arteries anastomose with the short posterior ciliary arteries in the equatorial region of the eye. Some observers have held that this anastomosis is poor and that its poor quality accounts for the early development of ring scotoma in retinitis pigmentosa. However, Wybar[49] has shown by study of neoprene latex casts, that this anastomosis is exceedingly rich.

The rabbit has been the animal most frequently used in recent years for studies of the choroid *in vivo*. Many similarities and some dissimilarities appear to exist between the uveal tract of man and that of the rabbit. According to Passera[33], the rabbit appears to be the mammal in which the structure of the choriocapillaris most closely approaches that of man. The rabbit does not have an anterior ciliary artery and consequently the anterior uveal tract is supplied by the long posterior ciliary artery. The venous return of the choroid originates in the vortex veins, which comprise two upper and two lower vortices in most higher vertebrates. In rabbits, however, these veins are situated considerably more anteriorly. In man, the ophthalmic division of the internal carotid artery furnishes the sole blood supply to the uveal tract. However, in lower animals there is an equally large anastomotic branch from the external carotid artery, so that the ocular circulation of the rabbit arises from both the internal and external carotid arteries.

RELATIONSHIP OF ARTERIES TO ARTERIOLES. Unanimity of opinion does not exist as to the criteria by which to distinguish small arteries from arterioles. Kernohan and co-workers[24] stated in 1929 that they had "been unable to find in the literature on anatomy actual measurements of the outside diameter of the small vessels, which would permit an accurate measurable distinction between small arteries and arterioles." They arbitrarily chose 100 microns as the upper limit of diameter of an arteriole and Ham[22] expressed agreement with this. Landis[26], on the other hand, referring to the mesenteries of small mammals, regarded as arterioles vessels ranging in diameter from 15 to 35 microns; he considered all larger vessels to be small arteries. Cowdry[15], however, placed the upper

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limit of diameter of arterioles at 150 microns and stated that there is relatively more of the muscular coat in the arteriole than in any other segment of the vascular apparatus. The presence of this muscular coat provides for regulation of the blood flow into the capillaries, so that the blood enters the capillary bed in an even stream rather than in pulsations. Cowdry stated that the term *arteriole* is justified if the vessel exhibits a complete layer of typical, fusiform, smooth-muscle cells. Best and Taylor[6] appeared to agree with this view and regarded arterioles as being, on the average, less than 200 microns in diameter. They stated that the "walls are thick and composed almost entirely of smooth muscle lined by an endothelial layer and sheathed by scanty adventitia." They noted that the arterioles, after a variable distance, lose their muscular and connective tissue and continue as capillaries, 2 to 18 microns in diameter. However, to Baker[4,5] the muscular coat is difficult to find in cerebral arterial vessels of less than 70 microns in diameter. Friedenwald[19] and Adler[1] both defined arterioles as small arteries which do not possess an internal elastic lamina or a continuous muscular coat.

Summation of this problem appeared in the article by Moritz and Oldt[32] in which they stated, "no satisfactory definition of an arteriole was found, other than that the smallest arteries are arterioles. A variety of criteria have been proposed to distinguish between small arteries and arterioles. . . . These include the number of layers of smooth muscle in the media, the existence of an internal elastic lamella and the external cross-sectional diameter of the vessel. We have not found any of these distinctions useful and propose to use the terms *arteriole* and *small artery* interchangeably." Their investigation was directed at vessels with an outer diameter of less than 100 microns.

Terminal arterioles and metarterioles may be considered to be those vessels that are less than 30 microns in diameter and that are separated from the capillaries by precapillary sphincters, which also contribute to the regulation of blood flow in the capillaries[23]. The existence of sympathetic vasoconstrictor fibers in the choroidal arteries has been demonstrated[13,35]. The role of the pericytes recently discovered in the choroidal precapillaries, capillaries and postcapillary veins, in the regulation of blood flow in the choroid, remains to be determined[46].

EXPERIMENTAL APPROACHES TO STUDY OF THE CHOROIDAL CIRCULATION. Until recent years, information about the choroidal circulation was obtained indirectly through the effect of various drugs on the intraocular pressure[2,14,16,30,39,41]. So many other factors enter into control of intraocular tension that this appears to be an inadequate method for evaluating changes in the choroidal vessels. Bothman and Cohen[10,13], and later Matteucci[31], observed the choroidal vessels with the ophthalmoscope after administration of various drugs. Later, Zwiauer and Bornschein[9,51] studied the choroidal circulation by a technique similar to Lambert's[25], in which a contact lens was placed over the cornea and the fundus was viewed with a microscope. However, these methods were dependent on good mydriasis, which caused another drug to be introduced into the experiment; some administered drugs cause the pupil to contract and this makes observation of the fundus difficult. Also the magnification is limited and it is almost impossible to maintain fixation on any single vessel and to distinguish arteries from veins with accuracy.

Schurr[42], in 1951, described angiography of the ophthalmic artery and

the choroidal arteries by introduction of iodopyracet (Diodone) into the common or internal carotid arteries. While this was painful to human subjects, the dye was visible in the choroid on rapid radiograms in 10 of 17 patients. Schurr[42] advocated development of this method for study of vascular disease. François and associates[18] similarly produced excellent radiograms of the choroidal, as well as the retinal vessels in enucleated eyes by using a colloidal suspension of thorium dioxide (Thorotrast).

In 1952, Vilstrup[45] injected a plastic material into both carotid arteries of the living rabbit. The material solidified rapidly, killing the animal and forming a cast of the choroidal vessels. After local instillation of a drug into one eye, Vilstrup was able, by histologic methods, to compare the effect on the choroidal capillaries and arterioles of the treated eye with the effect on the same vessels of the untreated eye. However, this injected material produced a violent muscular spasm before death, and readily could have altered the circulatory flow and the status of the vessels.

Leopold[27], in 1951, was the first to introduce scleral windows that permitted a direct microscopic view of the choroidal circulation in the albino rabbit. Greaves and Perkins[21]; Wudka and Leopold[47,48]; Stein, Wakim and Rucker[44], and Paul and Leopold[34] subsequently have done studies by dehydration of the opaque sclera. Dehydration makes the sclera transparent and the underlying choroidal vasculature becomes visible. This technique permits repeated measurements of the diameter of the blood column, or lumen, of the vessel. Although this transcleral view is excellent, and although high magnification can be achieved and easily reproducible photographic evidence can be obtained, it is difficult to evaluate the disturbance in the physiology of the choroidal circulation resulting from the trauma of insertion of the windows or from dehydration of the overlying sclera. The techniques mentioned in this paragraph give a value primarily for the luminal diameter of the choroidal vessel.

Perkins[35], in 1955, inserted a small thermocouple in the region of the ciliary body of the rabbit and recorded changes in temperature which were considered indicative of changes in blood flow in this region.

Bettman and Fellows[7,8], in 1956, introduced a new technique designed to determine blood volume in the ocular circulation. By labeling the red blood cells of cats with radioactive phosphorus, the investigators were able to compare the radioactivity in the ocular circulation after various drugs had been introduced; this technique evaluated changes in blood volume. This method, however, does not enable one to differentiate the effect on the retina from that on the choroid, or to identify the isolated effects on the capillary, arteriole or artery in the choroidal vascular bed.

GENERAL MECHANISM OF ACTION. Autonomic drugs can be classified as to their ability to stimulate or destroy cholinergic or adrenergic impulses. An excellent review of their general effects has been reported by Wudka and Leopold[48].

Parasympathomimetic drugs either augment the established function of the effector cells at the parasympathetic nerve endings or interfere with the action of the enzyme, cholinesterase, which destroys the acetylcholine produced at the myoneural junction. Pilocarpine is representative of drugs that have the former effect; it acts directly on the effector organs, mimicking the effects of postganglionic cholinergic nerves. Drugs that interfere with the

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action of cholinesterase can be divided into those that produce a reversible inactivation of cholinesterase, such as eserine (physostigmine) and neostigmine (Prostigmin), and those that combine irreversibly with cholinesterase, such as di-isopropyl fluorophosphate (D.F.P.)[28,29].

It is believed that eserine acts by protecting acetylcholine from the destructive action of cholinesterase. Consequently, in the presence of eserine, the action of acetylcholine is prolonged. Acetylcholine administered intravenously has been known to cause vasodilatation in the skin of man and, when administered intra-arterially, dilatation of the regional arteries and arterioles[20]. However, because of its transient and ill-sustained action in the body, methacholine, carbamylcholine and other congeners have been developed.

Drugs that act on the effector organs and block the transmission of cholinergic impulses are called *parasympatholytic drugs* (cholinergic blocking agents). Atropine, scopolamine, methantheline (Banthine), oxyphenonium (Antrenyl) and cyclopentolate (Cyclogyl) belong to this group. These drugs act directly on the effector organ so as to block the action of the acetylcholine that is released at the myoneural junction.

Sympathomimetic drugs exert their effect by acting directly on the effector organ. The chemical substance liberated at the effector organ "appears to be similar to if not identical with epinephrine or perhaps norepinephrine, also called arterenol"[27]. Epinephrine has been shown to constrict the arterioles and the precapillary sphincters when applied topically to the mesoappendix of the rat[12]. Although extensive research has been done on the fate and excretion of epinephrine, much that is uncertain yet remains to be clarified. At present it is believed that "epinephrine is degraded in the body by two enzymatically activated mechanisms, conjugation and oxidation"[20]. The former is the more important process and occurs in the liver and intestine. Of lesser importance is the destruction by oxidation, through the action of the enzyme, amine oxidase. Philpot[36] expressed the belief that cocaine exerts its sympathomimetic effects by inactivation of amine oxidase. However, Cannon and Rosenblueth[11] offered two explanations for the sympathomimetic action of cocaine: 1) Cocaine may prevent the destruction of epinephrine or of chemical mediators released by adrenergic nerves. 2) Cocaine may increase the permeability of sympathetically innervated cells and thus favor the entrance of the stimulating agent.

Sympatholytic (adrenergic blocking) agents such as tolazoline (Priscoline) block the response of effector cells to adrenergic impulses.

Ganglion-blocking agents, such as hexamethonium and pentolinium (Ansolysen), are capable of interfering with impulses at both parasympathetic and sympathetic ganglia. "They act either by preventing depolarization of the cellular membrane of the postganglionic neuron or by producing a prolonged depolarization with an associated absolute refractory state"[38].

Drugs that act directly on the end-organ include the nitrites, which cause smooth muscle to relax, particularly muscle of the finer blood vessels, and hence produce vasodilatation and a fall in blood pressure. Preparations of histamine also act directly on the effector cells. In man and animals, histamine causes capillary dilatation. However, the effect on arteries and arterioles varies considerably and, in the lower animals, these vessels usually undergo vasoconstriction[20,40]. The xan-

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TABLE 1.—INFLUENCE OF DRUGS* ON THE CHOROIDAL CIRCULATION

Drugs tested	Leopold, 1951†	Wudka and Leopold, 1956	Stein, Wakim and Rucker, 1956	Bettman and Fellows, 1956	Paul and Leopold, 1956
I. *Parasympathomimetic*					
Acting on effector organ					
a. Pilocarpine	Topical: no effect	Topical and iv: no effect except secondary to systemic effect			
b. Carbachol (Doryl)	Iv: no effect; intravitreal: no effect	Iv: no direct effect; topical: no direct effect			
c. Methacholine (Mecholyl)	Iv: no effect; intravitreal: no effect	Iv: no direct effect		Iv and retrobulbar: decrease in blood volume "probably secondary to systemic effect"	
d. Bethanechol		Iv: no direct effect			
Anticholinesterase					
a. Eserine (physostigmine)	Topical: no effect	Topical: no direct effect; iv: no direct effect			
b. Neostigmine (Prostigmin)	Topical: no effect	Iv: no direct effect			
c. Di-isopropyl fluorophosphate (DFP)	Topical: no effect	Topical: no direct effect			
II. *Parasympatholytic* (cholinergic blocking agents)					
a. Atropine	Iv: no effect	Topical: no direct effect; iv: no direct effect			Retrobulbar: no effect
b. Scopolamine	Iv: no effect	Topical: no direct effect; iv: no direct effect			
c. Methantheline (Banthine)	Iv: no effect	Iv: no direct effect			
III. *Sympathomimetic*					
Acting on effector organ					
a. Epinephrine	Intravitreal: no effect; iv: no effect	Topical: constriction; iv: constriction; intravitreal: constriction	Iv: constriction; intra-arterial: constriction, blanching of choriocapillaris	Iv: increase in blood volume; retrobulbar: blood volume increase "possibly from secondary systemic effect"	
b. Arterenol (norepinephrine)		Iv: constriction; topical: constriction			
c. Ephedrine		Iv: vasoconstriction			
d. Phenylephrine (Neo-synephrine)		Topical: vasoconstriction			
e. Methoxamine (Vasoxyl)		Iv: vasoconstriction			
Amine oxidase inhibitor					
a. Cocaine		Topical: no effect			
IV. *Sympatholytic* (adrenergic blocking agents)					
a. N,N-Dibenzyl-β-chloroethylamine (Dibenamine)	Iv: no effect	Iv: no direct effect			
b. Tolazoline (Priscoline)	Iv: no effect	Iv: no direct effect		Retrobulbar: increase in blood volume; iv: decrease in blood volume secondary to sys-	Topical, retrobulbar, iv, intra-arterial: no effect

b. Tolazoline (Priscoline)	Iv: no effect	Iv: no direct effect		Retrobulbar: increase in blood volume; iv: decrease in blood volume secondary to systemic effect	Topical, retrobulbar, iv, intra-arterial: no effect
c. Phentolamine (Regitine)		Iv: no direct effect			
d. Piperoxan (Benodaine)		Iv: no direct effect			
e. Ergotamine	Iv: no effect	Iv: no direct effect			
f. Ergotoxine		Iv: no direct effect	Iv: no direct effect; intra-arterial: no direct effect		
g. Ergonovine		Iv: no direct effect			
V. *Ganglion blocking agents*					
a. Hexamethonium	Iv: no effect	Iv: no direct effect	Iv: no change if head horizontal; increased blood volume if head lowered, decreased if head elevated		
b. Tetraethylammonium	Iv: no effect	Iv: no direct effect (effects secondary to systemic effect)			
VI. *Direct acting*					
a. Histamine	Intravitreal: no effect; iv: no effect	Topical: vasoconstriction; iv: vasoconstriction; intravitreal: vasoconstriction	Iv: no effect; intra-arterial: no effect	Retrobulbar: decrease in blood volume	
b. Nicotinic acid	Iv: no effect	Iv: no direct effect	Iv: no direct effect; intra-arterial: no effect	Iv: no effect; retrobulbar: increase in blood volume	
c. Amyl nitrite		Inhalation: no effect		Inhalation: effect secondary to systemic effect	
d. Glyceryltrinitrate		Topical: no effect			
e. Sodium nitrite			Iv: no effect; intra-arterial: no effect	Iv: no direct effect on blood volume	Iv: no effect
f. Vasopressin (Pitressin)	Iv: no effect	Topical: vasoconstriction; iv: vasoconstriction			
g. Aminophylline	Iv: no effect	Iv: no direct effect		Iv: no effect; retrobulbar: increased blood volume	
h. Procaine				Retrobulbar: no effect in small doses, increased blood volume in large doses	Retrobulbar: no effect

* Table includes agents used by two or more observers and a few important agents used by only one observer.

† 1. In 1949, the positive findings of Zwiauer and Bornschein were blanching of the fundus background with epinephrine and vasopressin (Pitressin).
2. In 1952, Vilstrup noted vasodilatation with histamine administered topically and intravitreally; pilocarpine and epinephrine gave no effect.
3. In 1952, Greaves and Perkins found constriction of the choriocapillaris on intravenous injection of epinephrine.

thines, which include caffeine, theophylline (aminophylline) and theobromine, act in varying intensity, either by directly dilating the peripheral vessels through action on the musculature or by stimulating the medullary vasomotor center to bring about vasoconstriction.

ACTION OF DRUGS ON THE CHOROIDAL CIRCULATION. Recent investigators have administered pharmacologic agents to animals by a variety of routes (Table 1). Direct effect on the caliber of vessels was not obtained with any of the direct-acting parasympathomimetic agents (pilocarpine, carbachol [Doryl], methacholine [Mecholyl], bethanechol)[27,45,48] or anticholinesterase agents (eserine, neostigmine, di-isopropyl fluorophosphate)[27,48]. Bettman and Fellows[8], however, noted decreased blood volume with methacholine (Mecholyl) and acetylcholine, given intravenously or in the tissues behind the eye. From the studies of Wudka and Leopold[27,48], it seems evident that parasympatholytic drugs tested (atropine, scopolamine, methantheline [Banthine]) do not have any direct effect on the caliber of the choroidal vessels.

Epinephrine, representative of the sympathomimetic drugs, has been most frequently studied. Bothman and Cohen[10,13], in 1927, detected vasoconstriction of the choroidal arteries followed by vasodilatation. With epinephrine, Greaves and Perkins[21] noted constriction of the choriocapillaris, although Vilstrup[45] could not detect changes. Leopold[27], in 1951, was unable to detect any changes when epinephrine was injected both into the vitreous and into the veins of albino rabbits. However, in a subsequent article, Wudka and Leopold[48] reported vasoconstriction of the long posterior ciliary artery when epinephrine was injected intravenously and into the vitreous, as well as when it was applied topically. The earlier negative findings may possibly have been due to the fact that the scleral windows originally were inserted superiorly, where they overlay a preponderance of veins, rather than on the horizontal meridian, where they overlay the arterial aspect of the choroidal circulation. Stein, Wakim and Rucker[44] found definite vasoconstriction in the smaller arterial vessels when epinephrine was administered intravenously or when it was introduced directly into the carotid artery on the same side as that of the vasoconstriction. Also, blanching of the underlying choriocapillaris occurs with epinephrine[21,37,44]. Bettman and Fellows[8], on the other hand, noted an increase in blood volume when epinephrine was administered intravenously or in the tissues behind the eye. They considered this to be possibly from passive dilatation resulting from systemic effects of the drug. Other sympathomimetic drugs (arterenol [norepinephrine], ephedrine, phenylephrine, methoxamine [Vasoxyl]) have been tested topically and intravenously[48] and have been found to produce vasoconstriction of the long posterior ciliary artery.

Sympatholytic agents (see Table 1) have been studied by Leopold[27] and by Wudka and Leopold[48] but direct effect on choroidal circulation has not been detected. Similarly, Stein, Wakim and Rucker[44] could not detect changes in the smaller arterial branches with use of ergotoxine in observations extending more than 30 minutes. Bettman and Fellows[8], however, noted an increase in blood volume 20 minutes after tolazoline (Priscoline) had been injected into the retrobulbar tissues. A control retrobulbar injection of small amounts of saline solution did not cause change but injection of a larger amount resulted in blood volume being decreased by mechanical

pressure. Paul and Leopold[34], however, were unable to detect any changes in the choroidal vessels after tolazoline (Priscoline) had been administered topically, intravenously, behind the eye or intra-arterially. Their observations extended for 1 hour.

From the ganglion-blocking agents (hexamethonium, tetraethylammonium) administered intravenously, Wudka and Leopold[48] observed only effects secondary to systemic changes in blood pressure. Bettman and Fellows[8] did not note any effect from hexamethonium when the animal's head was horizontal but they observed decreased blood volume when the head was elevated and increased blood volume when the head was lowered.

Reports in ophthalmic publications concerning effects of histamine are conflicting. Wudka and Leopold[18] found that, after retrobulbar injection of histamine, vasoconstriction of the long and short posterior ciliary arteries occurred in less than 1 minute, while Bettman and Fellows[8] noted decrease in blood volume in the eye of the cat but did not state the period of time. However, Vilstrup[45] reported profound vasodilation of the choroidal capillaries and terminal arterioles of the albino rabbit after topical instillations and injections into the vitreous. Stein, Wakim and Rucker[44] were unable to detect any change in the smaller branches of the choroidal vessels after histamine diphosphate had been administered intra-arterially or intravenously.

Vasopressin has been found to produce vasoconstriction of the long and short posterior ciliary arteries, along with vasoconstriction of the choroidal arterioles[48]. Zwiauer and Bornschein[51] noted blanching of the fundus but no measurable change in caliber of vessels after vasopressin had been administered.

The nitrites as a group were not found to have any direct effect on the choroidal circulation by any of the investigators who employed them in a variety of forms and routes of administration[8,34,44,48,51].

Nicotinic acid did not produce detectable changes on the caliber of choroidal vessels when it was administered intravenously[44,48] or intra-arterially[44], but Bettman and Fellows[8] found an increase in blood volume after retrobulbar injections. Wudka and Leopold[27,48] could not detect that aminophylline influenced the caliber of blood vessels, while Bettman and Fellows[8] found an increase in blood volume after retrobulbar injections of the preparation.

Bettman and Fellows[8] found increased blood volume, indicative of vasodilatation, after retrobulbar injection of procaine. However, Paul and Leopold[34] could not detect changes in a large number of animals observed for 1 hour after retrobulbar injection of procaine.

The effect of inhalation therapy on the ocular circulation has been studied in experimental animals. No primary effect from amyl nitrite has been found[8,48,51]. Neither Bettman and Fellows[8] nor Paul and Leopold[34] detected any change in the choroidal vessels from high concentrations of oxygen. Bettman and Fellows[8] reported vasodilatation when carbon dioxide was inhaled in a concentration of 8 to 10%.

COMMENT. From reports published to date, it seems apparent that the response of the choroidal vasculature to drugs differs in many respects from the known effects of the drugs on the peripheral circulation. The basis of this difference is not readily apparent. The arterial branch chosen for study varied with the various experimenters and this may account for the difference in

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some of their conclusions. Vilstrup[45] measured the capillary network and the terminal arterioles. Wudka and Leopold[47,48], on the other hand, found vasoconstrictive changes in the long posterior ciliary artery, of which the diameter is 150 to 250 microns. Stein, Wakim and Rucker[44] found vasoconstrictive changes in arterial branches measuring 36 to 100 microns in inner diameter. Bettman in discussion of Bettman and Fellows[8] wrote: ". . . in cats the volume of retinal blood supply . . . was only 3 to 4% that of the choroidal blood supply." The effect they observed may be chiefly in the choriocapillaris, which contains the greatest volume of the various circulatory components which were studied. Also, perhaps technical factors inherent in the various techniques employed may be responsible for some differences.

From studies *in vivo* on the choroidal circulation, only vasoconstrictive changes were detected in the larger arterial branches by direct observation[44,48]. Porsaa's[37] contention, that the vasoconstrictive effect of epinephrine on the retinal vessels of cats was simply a mechanical reflection of the change in blood pressure, cannot be entirely excluded from consideration when epinephrine is given intravenously. When epinephrine was given intra-arterially, however, the peak vasoconstrictive effect occurred in 30 seconds, while the blood pressure did not become elevated until 50 seconds after injection[43]. This suggests primarily direct action of epinephrine on the arterial wall.

Definite vasodilatation of large arterial branches has not been observed directly as yet. However, there is still a relative paucity of reports and perhaps, considering the recently renewed interest in the choroidal circulation, some vasodilating drugs may be forthcoming. Assuming that the preponderance of blood volume as determined by the technique of Bettman and Fellows[7,8] lies in the choriocapillaris, then they have demonstrated that vasodilation follows retrobulbar injections of tolazoline (Priscoline), nicotinic acid, aminophylline and large doses of procaine. These effects occurred in 10 to 25 minutes after the injection. Although retrobulbar injection of other agents they employed produced systemic changes that resulted from absorption, Bettman and Fellows[7,8] suggested that the drugs named have direct action on the vascular bed. Paul and Leopold[34], however, in their search for choroidal vasodilators, were unable to discover any dilatation of the choroidal vessels caused by drugs administered by a variety of routes. In addition to the previously mentioned agents, cobra venom, typhoid vaccine, papaverine and adenosine triphosphate failed to produce any choroidal changes[34].

Wudka and Leopold[48] noted a focal type of constriction of the long posterior ciliary artery with use of epinephrine and arterenol (norepinephrine) and vasopressin (pitressin). This is interesting inasmuch as the smaller arterioles of the retina react in the manner described in hypertensive disease. Friedenwald[19] has noted that there are irregular patches of muscle in the retinal vessels and that these may permit a focal type of constriction. It is difficult to explain why the long posterior ciliary artery, which has a well-developed continuous muscular coat, should react in this localized and focal manner.

Summary. The availability of recently improved methods for study of the choroidal vasculature has renewed interest in this vital structure of the eye. By direct observation *in vivo* of

the choroidal vessels of experimental animals, sympathomimetic drugs have been found to produce vasoconstriction of the long posterior ciliary artery and the smaller choroidal arterial branches. The ability of these vessels to dilate has not as yet been observed directly, although some indication is available that the total blood volume of the eye may be altered if certain drugs are administered in the tissues behind the eye.

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PHYSIOLOGY

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SEMINAR ON HYPOTHERMIA

Temperature Regulation of Rats in Hypothermia. F. H. JACOBSON, PH.D. (Department of Physiology, Jefferson Medical College). The separate roles of falling, and constant low, body temperature in stimulating the vasomotor and thermogenetic responses of the white rat have been assessed.

Peripheral vasoconstriction (indicated by conductance measurements) was induced by constant low body temperature, the degree being a function of the level of temperature. At any temperature, the degree was further increased initially when the temperature was falling, and was decreased when the temperature was rising, although it might be altered to meet the tissue blood-flow requirements of elevated metabolism.

Heat production was not significantly correlated with constant body temperature unless "corrected" to normal temperature according to the Q_{10} law. Heat production was always significantly increased when an already low temperature was caused to decrease further. The likelihood exists that the adequate stimuli for suprabasal heat production and vasoconstriction are identical, but that the former response is impaired by low tissue temperature.

The effects of skin and deep temperature were not always well-separated, but evidence has been obtained for the existence of temperature receptors in deeper portions of the body, as well as in the skin, having similar sensitivity and response characteristics.

Cycles of colon temperature in animals exposed to constant environments have been described. These resemble the cycling of temperature in a physical model of the "proportional-position" type provided with an "automatic reset" although "resetting" may occur only because of a wide distribution of temperature receptors.

Hypothermia in Prevention of Ischemic and Hemorrhagic Shock.* W. M. PARKINS, PH.D., S. J. LEBRIE, PH.D., AND H. M. VARS, PH.D., (Harrison Department of Surgical Research, University of Pennsylvania). Healthy beagle hounds, under Nembutal anesthesia, were used in these studies. A visceral cooling method consisting of rapid intraperitoneal administration of 1 to 5° C. saline, designed for rapid, differential reduction in temperature and O_2 demand of the intestine and other viscera has been employed in three shock-like states. This method, as compared with surface cooling, blood cooling, or differential hepatic hypothermia proved most effective in preventing ischemic shock and death following temporary occlusion of the thoracic aorta. When the iced saline was introduced just following the aortic

*Supported in part by Army contract DA–49–007–MD–511.

occlusion, all dogs survived after a 90- or 120-minute period of ischemia which was fatal to all normothermic controls including those receiving intraperitoneal saline at 37° C. Visceral hypothermia also prevented irreversible hemorrhagic hypotensive shock in some but not all dogs following shed blood replacement after 120 minutes. Survival rates increased from 0 to 24 hours in normothermic controls to 80% at 24 hours and 40% beyond 72 hours when iced saline was administered at the end of the initial hemorrhage to 30 mm. Hg. Antibiotics administered at the end of blood replacement in the hypothermic group have further increased the 72-hour survival. Visceral hypothermia prevented the irreparable hypoxial damage of a still more severe degree of ischemia induced by occlusion of the thoracic aorta in hemorrhagic hypotension, followed by blood replacement. Ninety per cent survived indefinitely after a 60-minute interval which was fatal to all normothermic controls.

Normal and Abnormal Physiology of the Nervous System During Hypothermia. H. L. Rosomoff, M.D. (Department of Neurological Surgery, Columbia University and the Naval Medical Research Institute, Bethesda, Md.) A study has been made of the effect of hypothermia upon the normal and abnormal physiology of the nervous system. The effect on normal physiology has been to produce a decrease in cerebral blood flow, a corresponding reduction in cerebral oxygen consumption, a diminution of intracranial pressure and brain volume, and a depression of neural electrical activity. In respect to abnormal physiology, it has been shown that hypothermia protects against cerebral infarction in the dog, if body temperature is 22 to 24° C. when an artery, such as the middle cerebral artery is *permanently* interrupted. Protection is also afforded if the artery is interrupted at normal body temperature, provided hypothermia is induced within 15 minutes of the occlusion and if a level of 24° C. or less is attained within a total elapsed time of 90 minutes. The development of brain swelling following experimental brain injury is aborted by hypothermia of 25° C. The pathology of the lesions is also affected in that there is less widespread destruction of neural elements, less hemorrhagic diathesis, and diminished host reaction to injury during hypothermia.

A Simple Mechanical Calibrator for the Ultra-Low-Frequency Ballistocardiographic Bed. Walter J. Gamble, A.B. (Department of Therapeutic Research, Hospital of the University of Pennsylvania). The simple method used to calibrate high-frequency tables cannot be used in low-frequency tables, because, when a force is applied in one direction, the bed moves quickly beyond the permitted range. This problem can be solved by rapidly reversing the force direction, but the rotating arms usually used for this purpose cannot be easily applied with the subject on the table because of the superimposed ballistocardiogram. The device to be described meets this need.

Force in the headward direction is applied by supporting a 140-gram weight over a pulley, and this is attached to the table by a long horizontal elastic band and a short thread. Force in the footward direction is supplied similarly. By means of a heavy pendulum attached to the rubber bands by threads, the force exerted on the table by first one and then the other of the rubber bands is interrupted, so that the bed is subjected to alternate headward and footward

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forces at intervals controlled by the length of the pendulum.

Because the long rubber band permits small changes of length with negligible changes in the force applied, a "square wave" force is produced which deflects the record by an amount easily measured and the difference is equivalent to 280 grams of force.

The use of the calibrator with a patient on the table produces a ballistocardiogram with two rapidly alternating base lines. The distance between the two easily visualized base lines represents 280 grams of force.

BOOK REVIEWS AND NOTICES

THE MANAGEMENT OF MENSTRUAL DISORDERS. By C. FREDERIC FLUHMANN, B.A., M.D., C.M., Clinical Professor of Obstetrics and Gynecology, Stanford University School of Medicine. Pp. 350; 121 ills. Philadelphia: W. B. Saunders Co., 1956. Price, $8.50.

DESPITE the fact that the physiologic processes underlying both normal menstruation and abnormal uterine bleeding are reasonably well understood, these phenomena seem to perplex modern physicians almost as much as they did our medical ancestors. Fluhmann's most recent book "The Management of Menstrual Disorders" provides a means by which any physician can orient himself with regard to the cause, study and management of women who bleed abnormally.

After an historical survey of attitudes toward menstruation the hormonal and neural mechanisms responsible for uterine bleeding are discussed. The menarche, menstrual disorders in adolescent girls and the normal cycle are then considered. Physiologic changes, such as basal temperature, peripheral vascular responses, sexual response, alterations in genital and extragenital structures and systemic disorders of the menstrual cycle, as well as the ovarian and uterine phases, are discussed. The next 9 chapters are concerned with the bleeding abnormalities, one with the climacteric phase and the final one with the clinical use of endocrine products.

Although the hormonal treatment of bleeding disorders is fully described, the individual who is looking for a cure-all preparation will find little help here. Fluhmann repeatedly emphasizes the fact that while bleeding can often be regulated artificially the abnormality can never be corrected until the underlying defect is discovered. He gives specific directions for the evaluation of each of the conditions he discusses and repeatedly mentions the emotional factors which may underlie any of these abnormalities.

Although a considerable portion of the book presents basic physiologic information and an analysis of experimental studies which often intimidate readers, the lucid and interesting manner in which it is presented should make it appealing to a wide audience. Strangely enough this book should be interesting and valuable to medical students, general practitioners and specialists, even those with a particular interest in menstrual disorders; all should find a goodly amount of new, interesting and useful information in it.

J. W.

THE NEUROSURGICAL ALLEVIATION OF PARKINSONISM. By IRVING S. COOPER, M.D., PH.D., Director, Department of Neurosurgery, St. Barnabas Hospital, Assistant Professor of Neurosurgery, New York University Bellevue Medical Center. Pp. 104; 68 ills. Springfield, Ill.: Charles C Thomas, 1956. Price, $8.50.

HOPELESS invalidism produced by progressive tremor and rigidity is not an uncommon condition. The failure of medical therapy to help appreciably these unfortunates has stimulated neurophysiologists and neurosurgeons to develop surgical procedures for relief. Since the actual cause and the neurophysiological pathways for this condition are not definitely known, many procedures at various levels (cortex, ansa lenticularis, globus pallidus, cerebral peduncle, and cervical spinal cord) have been tried with occasional brilliant results and more often temporary improvement. Thus, each procedure has had its momentary period of brilliance followed by relative obsolescence. While doing one of these procedures, Dr. Cooper accidentally injured and had to obliterate the anterior choroidal artery. The operation had to be abandoned and the incision closed. To his amazement, the patient had considerable relief of the tremor and rigidity. This led to deliberate closure of this vessel in a number of cases.

This monograph is a presentation of Dr. Cooper's technique and results in the surgical treatment of Parkinsonism.

The patients are divided into two groups. The first group of over 50 patients were operated upon by occlusion of the anterior choroidal artery on one or both sides and the second group of approximately 70 patients were treated by alcohol injection into the globus pallidus. The first procedure is preferred in patients with unilateral lesions while the second procedure is reserved for patients past 55 with bilateral symptoms.

Dr. Cooper's results are well documented with careful preoperative and postoperative studies and in some cases appear almost miraculous. He claims the resting tremor has been abolished in the extremity contralateral to the occluded artery in 65% of his cases and that rigidity has been lessened in 75%. Hemi-

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plegia has developed in only 3 patients out of 50. The mortality rate from the anterior choroidal operation has been approximately 10%. In the group which had been treated by alcohol injection of the globus pallidus, the mortality rate has been approximately 3%. He states that with this procedure tremors and rigidity have been satisfactorily alleviated in approximately 85% of cases.

Dr. Cooper's results appear promising. The final evaluation of his procedure awaits the test of time and the findings of other investigators. There are definite risks and complications from his procedures and as he points out, they should be done only by neurosurgeons well acquainted with the anatomy and pitfalls.

This monograph should be read by all interested in the problem of Parkinsonism.

M. S.

Die Pathologie des kindlichen Pankreas. By Dozent Dr. Med. Gerhard Seifert. Pp. 151; 109 ills., 21 in color. Leipzig: Georg Thieme Verlag, 1956. Price, DM 52.

In order to appreciate this excellent book one should compare it with the chapter on the pancreas in the textbook on Pathology of the Fetus and Newborn by E. L. Potter. It is profound and comprehensive. It begins with two chapters on the development, histology and physiology of the pancreas and on the peculiarities of the fetal and infantile pancreas. Another chapter deals with various disturbances of pancreatic secretion (dyschylia). But the bulk of the book is devoted to the various diseases of the pancreas which occur in children including malformation, cystic fibrosis, acute necrosis, pancreatitis, islet diseases, tumors, and the involvement of the pancreas in fungus diseases, infectious diseases, blood diseases, storage diseases, and nutritional diseases. The text is well written. It reflects the judgment of a mature investigator. The illustrations are superb. The bibliography comprises close to 1,000 references. It is felt that this book is a must for gastroenterologists as well as for pediatricians and pathologists.

W. E.

Das klinische Bild der Dauerfolgen nach Hirnverletzung. Arbeit und Gesundheit No. 60. By Doz. Dr. Med. Clemens Faust. Pp. 91; 5 ills. Stuttgart: Georg Thieme Verlag, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $1.85.

In this monograph, practitioners will find a useful summary of the permanent motor, sensory, vegetative, agnostic, apractic and psychiatric sequelae of cerebral injuries. The author emphasizes that such injuries induce not only a variety of focal symptoms but often grave personality changes, particularly if the base of the frontal and temporal lobes and of the diencephalon are affected. Further chapters deal with traumatic epilepsy, neuroses, expert testimony and methods of examination. Of interest is the observation of paradoxic reactions to various toxins, for example, excitement on administration of Evipan. The rules dealing with cancellation of driver's licenses in posttraumatic epileptics by R. Jung and Meyer-Micheleit deserve special study. Appearance of seizures without coma, demonstration of definite convulsive reactivity with generalized dysrhythmia or of focal seizure potentials are considered as sufficient indication for termination of the license.

E. S.

Secret Enemy. The Story of a Disease. By James Cleugh. Pp. 273. New York: Thomas Yoseloff, Inc., 1956. Price, $5.00.

This is a fascinating book even for one like the reviewer who has been intensely interested in syphilis for so many years. It is surprising, however, that such a volume would be written at a time when interest in this "secret enemy" and former scourge has reached the lowest level in history. It also seems courageous (foolhardy?) for a publisher to produce this work in the face of a "falling market" on syphilis literature. None the less, this survey from 1495 to the present, composed by a layman, about whom more personal data would be welcome, "has been designed to give the average man a clear idea of what syphilis has meant to the world in the past, thereby putting into his hands the one sure weapon with which to conquer this still 'secret' enemy." This is accomplished by data under the following headings: The Perspective. Prologue. The Dragon's Teeth (Soil and Seed). Contemporary Voices (Descriptive; Explanatory; Prescriptive). The Judgment of Fracastoro. Iron Harvest (Renaissance and Baroque; The Eighteenth Century; The Nineteenth Century; The Twentieth Century), Syphilis and the Law. Syphilis and Society, Syphilis and the Individual, and Epilogue.

Since this presentation is supposed to bring the subject up-to-date, it would be fairer, but perhaps less dramatic for the author's thesis, to emphasize the virtual wiping out of syphilis as a real problem in recent years; also

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the important American Cooperative Clinical Group Studies, the Boeck-Bruusgaard (Gjestland) data on untreated syphilis, the effort of the World Health Organization against treponematoses, and the new "Syphilis" or the problem of biologic false positive reactions to the tests for syphilis. In spite of these omissions, this is a valuable book even to physicians. H. B.

ELECTRODIAGNOSIS AND ELECTROMYOGRAPHY. Edited by SIDNEY LICHT, M.D., Yale University School of Medicine. Pp. 272; 90 ills. New Haven, Conn.: Elizabeth Licht, 1956. Price, $10.00.

THIS book is written for physicians by a number of physicians outstanding in their special fields of investigation. It should be of great help to those interested in physical medicine, physiology, neurology and neurosurgery and any practitioner that encounters peripheral nerve pathology. In electrodiagnosis, a current is admitted to a muscle to evoke contraction; in electromyography, a current is evoked from a muscle contraction.

A delightful chapter on history introduces the book. Instrumentation, theory, methods and interpretation are discussed in detail in the following chapters: Apparatus, physiology of skeletal muscle, motor points, routine electrodiagnosis, chronaxy, strength-duration curves, progressive and alternating currents, electromyography, electrical skin resistance. Particular mention should be made of the charts of motor points, dermatomes, cutaneous nerve distribution and segmental innervations. The electromyographic tracings represent a great variety of actual case records from a large hospital. There are brief but thorough chapters on electroencephalography and electroretinography. H. R.

MEDICAL ASPECTS OF TRAFFIC ACCIDENTS. Edited by HAROLD ELLIOTT, M.D. Pp. 519; illustrated. Montreal: Sun Life Assurance Company of Canada, 1955. Price, $7.00 plus $.25 postage.

THIS volume is a compilation of the papers presented at the Montreal Conference on the Medical Aspects of Traffic Accidents. Subjects covered include statistical data on traffic accidents, the role of the educator and industry in the prevention of accidents, descriptions of research programs being carried out, alcohol and behavior defects as a cause of traffic accidents, and suggestions for further investigation.

It is stated that accidents represent the third most common cause of death, preceded only by heart disease and cancer. The problem is considered from the standpoint of the vehicle and roadway as well as the driver and pedestrian. Some sections will be of particular interest to engineers, others to law enforcement agencies and legislators, and others to drivers and physicians.

This book should be of interest to a wide variety of people and professions, including all those interested in or active in accident prevention programs. R. B.

L'HUMEUR AQUEUSE ET SES FONCTIONS. By MARC AMSLER, FLORIAN VERREY AND ALFRED HUBER, University of Zurich. Pp. 397; 131 ills. and 11 color plates. Paris: Masson et Cie, 1955. Price, 5,000 fr.

THE authors of this interesting and informative book have succeeded in sorting and organizing a vast quantity of data concerning the normal and pathologic physiology of the aqueous humor. Although it is primarily intended as a critical review of the more recent advances in the understanding of this complex fluid, the text is liberally fortified by personal observations of the authors, both clinical and experimental. Of particular interest are the chapters on fluorimetric studies of the aqueous. Excellent illustrations emphasize that portion of the text devoted to the cytology and bacteriology of samples obtained by anterior chamber puncture of the living patient. The section on normal physiology contains a valuable review of recent studies utilizing radioactive isotopes. The large questions concerning the etiology and pathology of glaucoma and uveitis have been purposely omitted. H. S.

THE YEAR BOOK OF MEDICINE, 1956–1957. Edited by PAUL B. BEESON, M.D., CARL MUSCHENHEIM, M.D., WILLIAM B. CASTLE, M.D., TINSLEY R. HARRISON, M.D., FRANZ J. INGELFINGER, M.D., AND PHILIP K. BONDY, M.D. Pp. 744; 118 ills. Chicago: The Year Book Publishers, Inc., 1956. Price, $6.75.

THE articles abstracted in the current volume of this series are taken from journals received between May, 1955, and May, 1956. The material is presented in six major sections, respectively dealing with Infections, The Chest, The Blood and Blood Forming Organs, The Heart and Blood Vessels and Kidney, The Digestive System, and Metabolism.

The abstracts are prepared by well-recognized authorities and give a concise résumé of much important progress in the above indicated areas of medicine. Internists and residents in internal medicine will find much of interest in this volume. C. Z.

THE MANAGEMENT OF FRACTURES, DISLOCATIONS AND SPRAINS. By JOHN ALBERT KEY, B.S., M.D., Clinical Professor Emeritus of Orthopedic Surgery, Washington University School of Medicine and H. EARLE CONWELL, M.D., Associate Professor of Orthopedic Surgery, University of Alabama School of Medicine. 6th ed. Pp. 1168; 1123 ills. St. Louis: C. V. Mosby Co., 1956. Price, $20.00.

THIS reviewer was impressed with the first edition of this text. This, the sixth edition, continues in the same tradition. Tne authors cover the gamut of traumatology of fractures, dislocations and sprains in a most satisfactory manner. Management of these lesions may vary in different clinics, however the authors have confined themselves with procedures found to be of best advantage in their wide experience. Hence, the text is not an encyclopedia of treatment. It follows then that this book should have broad usage including medical students, internes, residents in surgery and orthopedics, busy general practitioners and medical men in industrial medicine.

The text is well illustrated and the description of treatment of the many injuries clear and concise. The section on injuries and workmen's compensation laws is timely.

This valuable text should be on everyone's shelf be he slightly or greatly exposed to injuries and their management. A. S.

PROCEEDINGS OF THE 6TH ANNUAL MEETING OF THE WORLD FEDERATION FOR MENTAL HEALTH. By Austrian Society for Mental Hygiene (ed.), Vienna. Pp. 149; Vienna and Bonn: Wilhelm Maudrich, 1956 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $3.50.

THIS volume contains a total of 26 addresses delivered at the sixth World Federation meeting in Vienna (August 16–22, 1953). The program of the meeting was arranged by Drs. M. K. el Kholy, president of the World Federation, and H. Hoff, president of the Austrian host society, and was focused on the following main topics: (1) history, objectives and recent progress of mental hygiene activities in Austria and other European countries, in the United States and in South America; (2) social service agencies and the problems of alcoholism; (3) the role of the family in the prevention of mental disorders; (4) etiology, symptomatology and treatment of schizophrenia; (5) psychiatric disorders in displaced persons; and (6) rehabilitation of physically handicapped children. Several Russian speakers criticized surgical procedures (especially lobotomy) as an "anti-physiological" method of therapy for schizophrenia and advocated prolonged sleep as the method of choice for this condition.

All reports are in German and without English summaries. K. A.

HISTOLOGICAL APPEARANCES OF TUMOURS. By R. WINSTON EVANS, T.D., B.SC.(LOND.), M.R.C.S.(ENG.); L.R.C.P.(LOND.). Pp. 773; 989 ills. Edinburgh and London: E. & S. Livingstone, Ltd., 1956 (Williams & Wilkins Company, Baltimore, U. S. Agents). Price, $17.00.

ALTHOUGH the book is entitled *Histological Appearances of Tumours*, it includes their genesis, their mode of spread and their clinical behavior. Obviously some of these features are briefly discussed, because of the volume of the material presented. In his preface, the author admits to excluding intracranial neoplasms and tumors of the female genital system, although tumors of the peripheral nervous system, including those of the sympathetic nerve chains and those of the chemoreceptor system are adequately covered, if the latter can be considered in this category.

The chapters are well oriented; the subject matter is written in a concise and succinct fashion and controversial material is fairly presented. The photomicrographs on the whole are excellent and the morbid microscopic fields selected for demonstration indicate extreme care and considerable thought in their selection. The references at the end of each chapter would seem to be representative of the key articles relating to those particular neoplasms.

As a matter of interest, Fig. 599 on page 419, which is described as a glycogen-rich squamous cell carcinoma of the tongue, is reminiscent of a metastatic clear cell adenocarcinoma from the kidney, although admittedly it lacks the vascularity and the alveolar septate pattern of that entity.

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While there are similar treatises in this field, this book should prove a valuable addition to the library of the surgical pathologist and should be of interest to the surgeon and to the clinician. The oncologist might find the material not entirely adequate for his purposes, but the references should compensate for such deficiencies. One important point running throughout the entire text, which should be stressed, is the need for correlation between the morbid microscopic appearance of a lesion and its clinical evolution. A. P.

THE PHYSIOLOGICAL FOUNDATION OF DENTAL PRACTICE. By L. L. LANGLEY, A.B., M.A., PH.D., LL.B., Department of Physiology, University of Alabama School of Dentistry, and E. CHERASKIN, A.B., M.A., M.D., D.M.D., Department of Oral Medicine, University of Alabama School of Dentistry. 2nd ed. Pp. 587; 192 ills. St. Louis: C. V. Mosby Co., 1956. Price, $9.75.

THE composition of this book tends to follow the trend in present-day dental education in emphasizing a thorough knowledge of the basic sciences as a firm foundation for the practice of dentistry; foreword states, "Dental education, until recent years, concerned itself primarily with technical training." The shortcomings of this type of education have become more evident as the scope of dental practice continues to expand. The dental clinician interested in his patient as a whole must look beyond purely reparative procedures and seek to find the answer necessitating therapy.

A careful reading of the various chapters in the book will afford the reader a basic understanding of the many problems encountered in practice. It is difficult for this reviewer to find any chapter in the book that fails to comply with the intent of the authors to present an easily read and applicable text devoid of much extraneous material frequently found in larger books.

The various dental specialty Boards now functioning as a part of dental education have stimulated interest in the basic sciences, and this book will fill a much required need for those seeking certification in advanced dental education and training.

It is illustrated by photographs and excellent drawings with supplemental readings suggested at the end of each chapter. The general dentist, as well as the dental specialist, will find a wealth of material clearly explained in the various chapters. J. C.

PAVLOV AND FREUD: I. IVAN P. PAVLOV: TOWARD A SCIENTIFIC PSYCHOLOGY AND PSYCHIATRY. By HARRY K. WELLS. Pp. 224. New York: International Publishers, 1956. Price, $3.50.

A STUDENT and admirer of Pavlov presents the teachings of the great physiologist to the American public, general and scientific, at a time when we are clutching wildly for answers to the problems of pathological deviations in human behavior. It appears that Pavlov tried to extend some very good work in reflex physiology into the realm of human behavior and account for complex phenomena without taking into account the necessity of a very complex psychological superstructure to explain the complicated behavior of mental illnesses. "When the equilibrium is upset by some big change in the conditions of life, the excessively strong stimuli resulting may, under certain conditions, break down the established balance between the excitatory and inhibitory processes. Neurosis then is a result of overstrain of the nervous system when the conditions of life have put too great strain on it" (p. 132). But the author never indicates that Pavlov understood what those strains were or when they occurred. Pavlov was insisting that the scientific world be content with a highly mechanized theory. He scorned emotion and ideas. He felt that such speculation was not helpful. "It may be that strong emotion was a contributing cause. To say that however is to lead nowhere" (p. 133).

The author says "The Pavlovian approach to psychiatry brings it back into the fold of medicine. It puts the emphasis not on the content of the mental symptoms but on the patho-physiological mechanism underlying them." All this sounds fine but quite apart from the author's qualifications for interpreting Pavlov (on which we are given no information). We have in this book the old plea for us to be satisfied with the idiom of the physiologist to account for aberrations in man's thinking and feeling. Physiology has its place of honor in the understanding of man and disease but it would appear that it was not Pavlov's destiny to contribute more than a small part to the total behavior of man. The author would have him do more but his book attempting this is not convincing. O. E.

SERVICES FOR CHILDREN WITH HEARING IMPAIRMENT. Prepared by the Committee on Child Health of the American Public

Health Association. Pp. 124. New York: American Public Health Assn., 1956.

THE American Public Health Association has performed a much needed service in publishing this book. Written clearly, in nontechnical language, the book surveys the areas of case-finding, diagnosis, and rehabilitation of children with auditory disorders. A community program for the hard-of-hearing child is outlined in some detail. All avenues of rehabilitation, including the medical, audiological, and educational, are reviewed. The ten Appendices add greatly to the value of this book.

The advisory group (no single author is indicated) contains an impressive array of distinguished names in the fields of otology, audiology, and education. Although the book is subtitled: *A Guide for Public Health Personnel*, it would be a very valuable addition to the library of any professional person who comes in contact with the hearing-impaired child. P. R.

DISEASES OF THE BREAST. By C. D. HAAGENSEN, M.D., Professor of Clinical Surgery, The College of Physicians and Surgeons, Columbia University. Pp. 751; 404 ills. Philadelphia & London: W. B. Saunders Company, 1956. Price, $16.00.

THIS book presents a very complete and accurate compilation of the diseases of the mammary gland. Included are sections on anatomy and physiology, the methods used in diagnosis of breast disease, benign diseases of the breast and carcinoma. The latter is given a great deal of space and its treatment is fully discussed including a rather detailed technical description of the Halstead mastectomy as modified by the author, complete with excellent illustrations.

The author of this book is well known as an outspoken authority on mammary carcinoma. One minor criticism might be that he presents his own personal views on the subject rather than a consensus of a group of authorities. There will be disagreement on a few details such as the importance of extremely thin skin flaps and routine skin grafting in radical mastectomy. Some will disagree with his criteria of operability. However, the author supports his views well and the bulk of the material is extremely accurate and well presented.

This book is recommended highly to all physicians who diagnose or treat diseases of the breast. R. B.

DIAGNOSTIC PROCEDURES FOR VIRUS AND RICKETTSIAL DISEASES. 2nd ed. Pp. 578; 49 ills. New York: American Public Health Association, 1956. Price, $7.50.

DURING the 8-year interval since publication of the first edition of this work, numerous advances have been achieved in the methods for laboratory diagnosis of viral and rickettsial diseases. Under the chairmanship of Thomas Francis, Jr., an outstanding group of investigators have delineated the pertinent methodology in their respective fields.

Tissue culture methods, adenoviruses, and ECHO (enteric cytopathogenic human orphan) viruses are among the new subjects considered. Information regarding the previously known viral and rickettsial agents has been brought up-to-date.

This volume will be helpful to all laboratory workers concerned with the diagnosis of diseases caused by these organisms. It will also be valuable to clinicians for general principles of diagnosis and the proper interpretation of observations made in the laboratory. C. Z.

ATLAS OF TUMORS OF THE NERVOUS SYSTEM. By H. M. ZIMMERMAN, M.D., M. G. NETSKY, M.D., AND L. M. DAVIDOFF, M.D., Montefiore Hospital, College of Physicians and Surgeons, Columbia University and Albert Einstein College of Medicine, New York City, Pp. 191; 277 ills, 233 in color. Philadelphia: Lea & Febiger, 1956. Price, $25.00.

THIS book should prove to be a welcome addition to the library shelf of the neuropathologist and neurosurgeon and should prove to be extremely valuable to the hospital pathologist, who sees infrequent neurosurgical material. The subject matter is presented in a brief and concise fashion and is entirely adequate, since the primary aim of the authors is to present a pictorial account of the gross pathological and morbid microscopic aspects of neoplasms of the central and peripheral nervous system. As might be expected the text is well illustrated by drawings, pictures of gross specimens and photomicrographs. The latter are all in color, except for eight, and on the whole are excellently reproduced, carefully selected and entirely representative. Some of the photomicrographs, namely Figs. 15, 43, 63, 94, 96, 222 and 223, while listed as hematoxylin-eosin stains are difficult to appreciate as such, since they lack definitive basophilic and eosinophilic properties, although this does

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not detract from their value in pointing out the pathology of the given lesion. The drawings are indeed excellent and the pictures of the gross specimens are adequately descriptive. The authors continue to use the classifications of Bailey and Cushing for gliomas and cite their objections to the more recent simpler nomenclature. The chapter on Congenital Tumors of the Brain is well covered and perhaps what some pathologists, including myself, have called subependymal glioma, is listed as nodular heterotopia (Fig. 155) by the authors. Comments on granulomas, which may be mistaken for tumors, and on the effects from increased intra-cranial pressure and of compression of the spinal cord are additional features. A distinction between cerebral swelling and edema is made. A few short paragraphs on tumors of the paraganglionic cells and a few statements relative to Roentgen irradiation of nervous system tumors complete the text.

A. P.

STRAIGHT TO THE HEART. BY GEORGE LAWTON, PH.D., with a special supplement by ETHEL LAWTON. Pp. 347. New York: International Universities Press, Inc., 1957. Price, $5.00.

THE reviewer, a cardiologist especially interested in cardiac surgery, admits frankly that he cannot detach his knowledge from his judgment so that he can appraise the effect this book will have on lay readers. He cannot therefore decide whether this book will do good, do harm or have no appreciable effect. His prejudice favors the last because the book has no literary worth and the author does not accomplish his intended task, namely "I felt it was my duty and responsibility to my fellow sufferers and to scientists to accurately present my remembered experience and reactions."

A book with such a purpose written expressively by an accurate observer with a retentive memory would indeed be worthwhile. Unfortunately, easily three-fourths of the book is devoted (in the common manner of a lay person ignorant of medicine yet worshipping his physician) to the not too subtle attempt to sell his surgeon to the reader. This theme is ubiquitous so that an unkind person may wonder whether the book was written by the surgeon rather than the patient.

The author, a 54-year-old psychologist who underwent apparently successfully an aortic commissurotomy, is a professional writer of the popular up-lifting type as indicated by the title of his previous books (*New Goals for Old Age, Aging Successfully, How to be Happy though Young*). It is, therefore, all the more incomprehensible that he did not stick to his expressed purpose.

The supplement by his wife is written in a more subdued tone. She will be pleased to know that her suggestion for the need of social workers and psychiatrists as ancillary aids in the over-all treatment of the cardiac surgical patients had already been anticipated and their services utilized in other clinics.

L. S.

AGOSTINI BASSI IN THE HISTORY OF MEDICAL THOUGHT. A. BASSI AND L. PASTEUR. BY GIOVANNI P. ARCIERI, M.D., Introduction by A. CORSINI. Preface by C. FRUGONI. Pp. 39; 6 ills. Florence: Leo S. Olschki, 1956. No price given.

THIS booklet, by a well-known Italian writer on medical history, now living in New York, traces the story of microbiology from the Romans to modern times. A good case is made out for the position of Bassi as the real founder of microbiology, rather than as a precursor of Pasteur, with his discovery of the microscopic organism that caused silkworm disease, *mal di segno* (published 1835). Of the many contributors to the concept of *contagium animatum* from Fracastorius on, Arcieri touches on some 20 or 30, nearly all Italians. This can well serve as a reminder to us of the very considerable role that Italy played in the biologic sciences from their beginnings to well into the 19th century.

E. K.

BLADDER TUMORS: A SYMPOSIUM. Under the auspices of the American Cancer Society. Pp. 92; 52 ills. Philadelphia: J. B. Lippincott Co., 1956. Price, $4.00.

THIS symposium reflects, for all intents and purposes, the opinions of its main contributor, Dr. Victor F. Marshall. It is primarily a collection of his previously published papers and contains essentially no new material. Whether one agrees or not with Dr. Marshall's management of bladder tumors, his work has been very stimulating and is of great value to urology. He has treated a tremendous number of cases and the evaluations of his operative results are honest and give the urologic surgeon a workable regimen for making a decision as to the management of bladder tumors. This book is recommended to the urologist who desires a complete ap-

praisal of the good work done by one group in the management of bladder neoplasms.

T. H.

EXPLORATION CLINIQUE DE LA FONCTION MUSCULAIRE ET BILAN MUSCULAIRE. By CH. ROCHER, formerly Chief of the Orthopaedic and Surgical Departments, now Chief of Kinesiotherapy and Director of Pedicure at the Hospital of Bordeaux, France. Pp. 175; 158 ills. Paris: Masson & Cie, 1956. Price, 1.800 fr.

DR. ROCHER is well qualified to give us the result of his long experience as far as evaluation and testing of the muscular system goes. After a short review of the muscular physiology and a recall of the principles of physics applied to the musculoskeletal system, the author says a few words about the clinical methods of exploration of the muscular function. Inserted are drawings of the trigger points of the muscles.

The main part of this book is devoted to the testing of the muscular system. In order to diminish as much as possible the subjective evaluation of the operator, the author gives a series of tests which he calls, "Test de controle de la puissance maxima des mouvements fondamentaux" based on the following principles: A) On the average healthy adult the muscular strength is usually adapted to the body weight. B) The power of a muscle is the function of the distance between its points of insertion. The author then uses a part of the body as resistance to be overcome by a muscle; on the other hand, he places this muscle in such a position of function that this motion can only be accomplished by a normal person. All of these tests are well explained and illustrated diagrammatically.

In pathological cases, the author proposes the methods of these tests which he describes in detail. The application of these tests is the answer to these three questions: 1) Does the muscle contract? 2) Does the muscle overcome the gravity represented by the weight of the distal segment of the limb? 3) Does the muscle overcome the gravity plus another weight? This evaluation is graded on a scale of 10 which gives a broader appreciation.

This book gives some additional information and new ways to consider the problem of muscular testing. It is valuable to those who are interested or confronted with the functionings of the musculo-skeletal system.

A. M.

CYTOLOGIC TECHNICS FOR OFFICE AND CLINIC. By H. E. NIEBURGS, M.D., Director, Cytology Laboratory, Beth El Hospital; Research Associate, Mount Sinai Hospital; Consultant and Lecturer Division of Cancer Control, Department of Health, New York City. Pp. 233; 177 ills. New York: Grune & Stratton, Inc., 1956. Price, $7.75.

THIS volume, as the author intended, presents all the steps in cytologic techniques from the time of cell collection to microscopic examination. Some of the more accessible areas of the body such as the oral cavity, larynx and skin would seem to lend themselves more easily to biopsy than to scraping or to abrasive methods as may be indicated. Interpretations of the normal and abnormal cells as found on the smears are briefly enumerated at the end of each chapter.

The illustrations comprise some of the methods of collection of the material and some of the normal and abnormal cells found on microscopic examination; these have been carefully selected and are graphic. This book is a valuable tome for the clinician and the cytopathologist and for those interested in cytologic techniques.

A. P.

PEDIATRIC CARDIOLOGY. By ALEXANDER S. NADAS, M.D., F.A.A.P., Professor of Pediatrics, Harvard Medical School. Pp. 587; 343 ills. Philadelphia: W. B. Saunders Co., 1957. Price, $12.00.

THIS book is a practical treatise on cardiac disease in infants and children. The author emphasizes that he has recorded his personal experience rather than attempted a comprehensive evaluation of the current literature. He has had an extensive clinical experience in a relatively brief period of time, and his writing indicates a maturity of clinical judgment. The book is well-written, in somewhat more of a conversational style than that of the usual text, a factor which increases the length somewhat but favors readability. One would deduce that the author is a good teacher and enjoys teaching.

Perhaps the strength of the book is in the section on congenital heart disease, which makes up a relatively large part of the manuscript. One weakness is the almost total absence of consideration of the psychologic management of the child with heart disease. The concentration is on the cardiac disorder rather than on the child with cardiac disease. Another lack is the failure to emphasize the current trend to "overdiagnosis" of rheumatic fever. And in this respect it would seem

that more emphasis might have been given to the "insignificant murmur."

The book should prove helpful to student and practitioner. W. N.

YEAR BOOK OF GENERAL SURGERY. Edited by EVARTS A. GRAHAM, A.B., M.D., Emeritus Professor of Surgery, Washington University School of Medicine; formerly Surgeon-in-Chief of the Barnes Hospital and of the Children's Hospital, St. Louis. Section on Anesthesia. Edited by STUART C. CULLEN, M.D., Professor of Surgery and Chairman of Division of Anesthesiology, State University of Iowa College of Medicine and Hospitals. Pp. 647; 157 ills. Chicago, Ill.: The Year Book Publishers, Inc., 1957. Price, $6.75.

As was true in previous years, this new edition of the "Year Book of General Surgery" is worthy of reading by anyone interested in surgery. The outstanding articles of last year's publications are well represented and arranged in an orderly fashion. Again there is a section devoted to articles on anesthesia. There are perhaps a few more abstracts on cardiovascular surgery as one would anticipate. The Editorial Comments are valuable additions to the excellent abstracts.

This volume might be considered as a very easily digested capsule containing the essence of the past year's surgical literature. R. B.

MENTAL HEALTH ADMINISTRATION. BY JACK R. EWALT, M.D., Commissioner, Massachusetts Department of Mental Health. Pp. 168. Springfield, Ill.: Charles C Thomas, 1957. Price, $5.50.

THIS book sketches briefly the ingredients of a complete mental health program.

It outlines concepts of administration, the role of administration in effecting good patient care, certain features of construction and maintenance of buildings. It discusses the role of various professional groups in the phases of mental health operation, cost and building budgets and the use of formulas for food and maintenance items. The reader gets an idea of the scope of the problem of administration, its basic goals and the rudiments of setting up and operating a mental health organization. O. E.

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